# Tofacitinib for Rheumatoid Arthritis

**Clare Kahn, Ph.D.**

**Vice President Worldwide Regulatory Strategy, Specialty Care**

**Pfizer, Inc.**

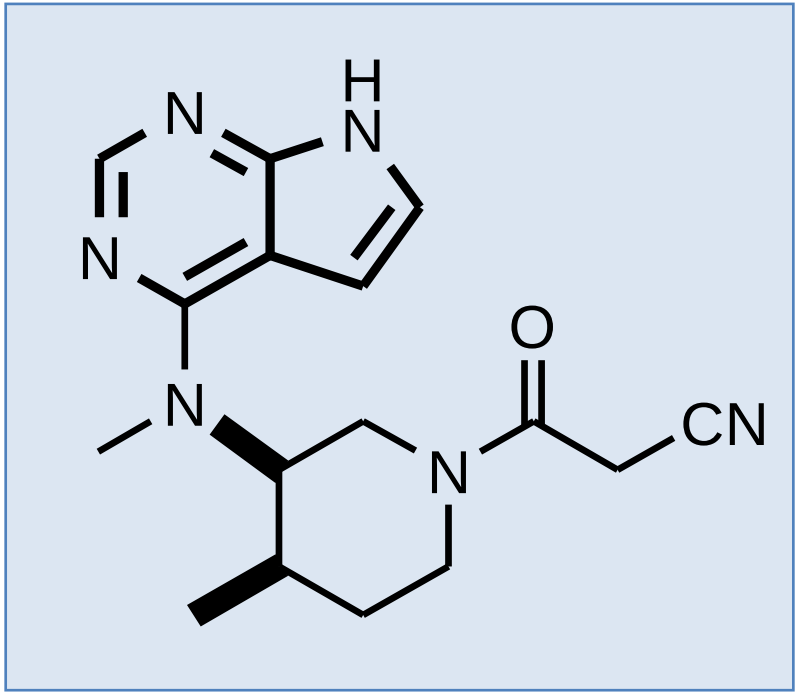
**Advisory Committee Meeting**

May 9, 2012
FDA White Oak Campus
Silver Spring, MD

# Tofacitinib is a Novel, Oral, Small Molecule Therapy for Rheumatoid Arthritis

**Potentially first new oral Disease Modifying Anti-Rheumatic Drug (DMARD) in more than 10 years**

**Tofacitinib**




Flanagan ME et al, *J Med Chem* 2010; 53:8468-8484

# Tofacitinib Developed and Studied to Meet Unmet Medical Need in Rheumatoid Arthritis

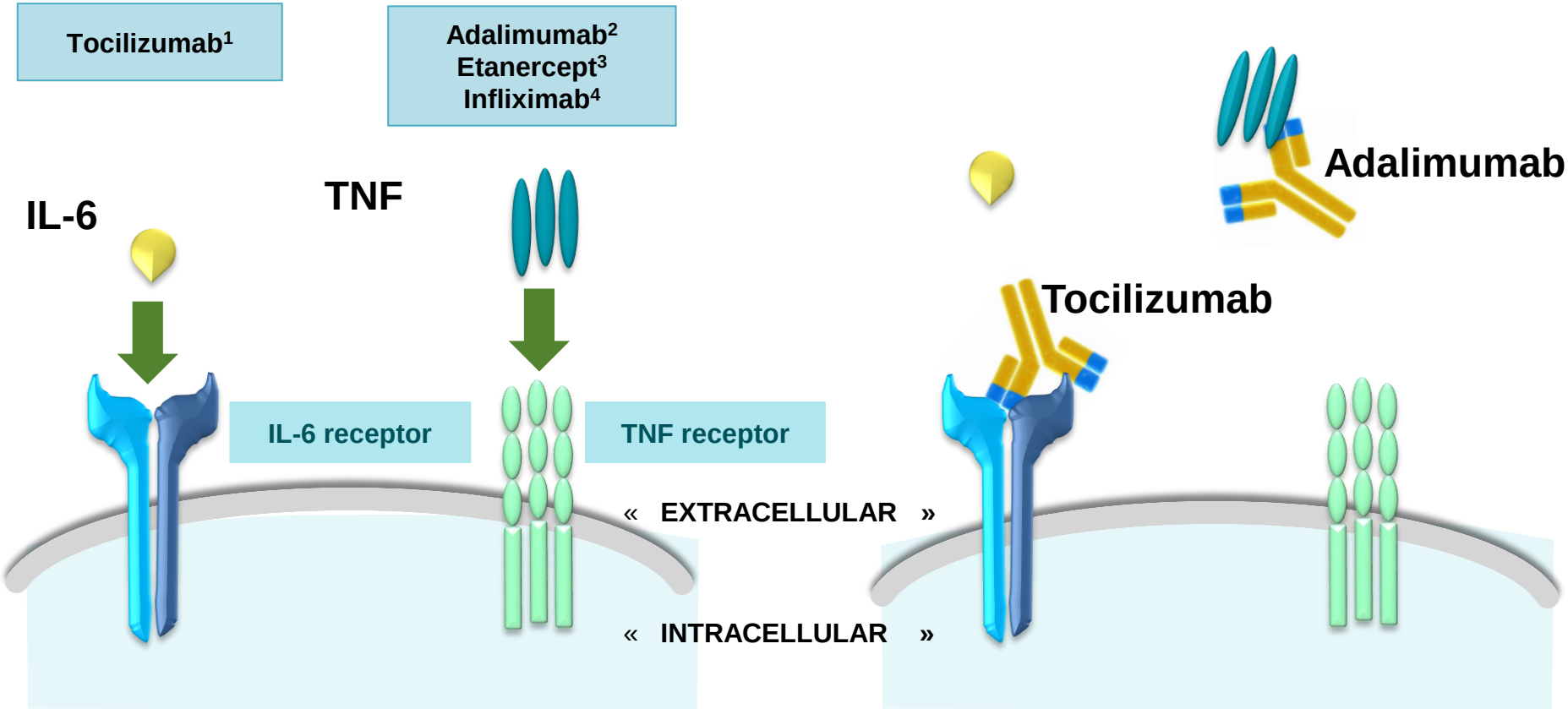
- Unmet medical need
  - Many patients fail to meet treatment goals with current therapies
- Development goal
  - Effective therapy with novel MOA and manageable safety profile
- Global clinical development program
  - 5 Phase 3 studies
  - Approximately 4800 patients with inadequate response to current therapies in the Phase 2 and Phase 3 program

# Pathophysiology of Rheumatoid Arthritis

- Systemic autoimmune disease
- Characterized by dysregulation of pro-inflammatory cytokines
- Cytokines regulate recruitment, retention, and activation of immune cells, leading to tissue inflammation and joint damage

McInnes IB, Liew FY. *Nat Clin Pract Rheumatol.* 2005;1:31-39

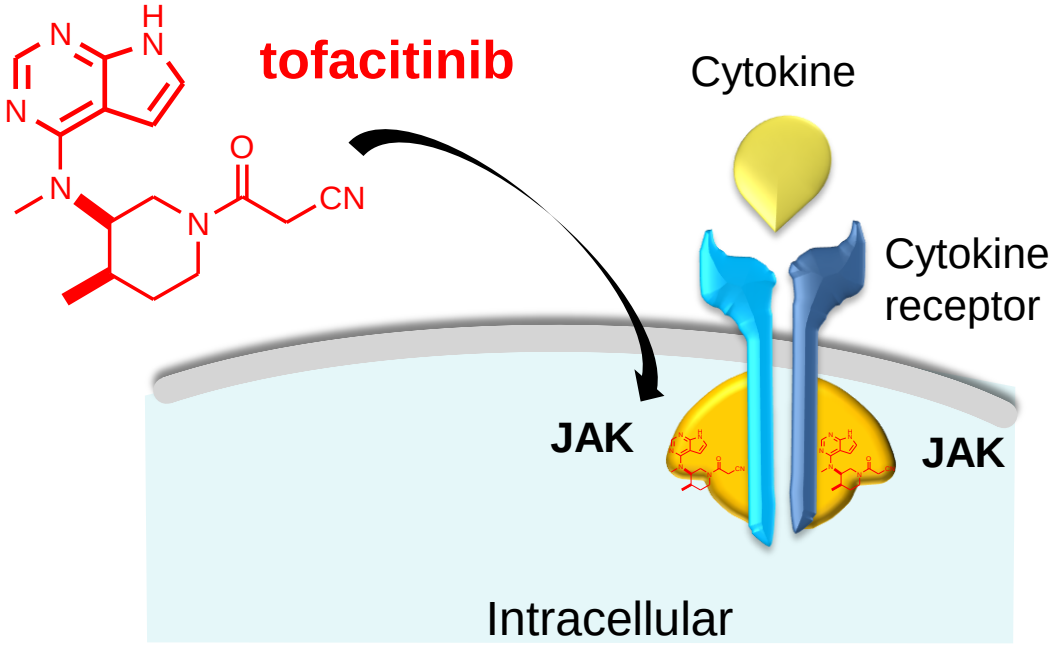
# Biologic DMARDs Target Single Cytokines in the Extracellular Space




IL=interleukin; TNF=tumor necrosis factor.

1. Actemra® (tocilizumab). Prescribing Information. Genentech, Inc. 2011; 2. Humira® (adalimumab). Prescribing Information. Abbott Laboratories. 2011; 3 Enbrel® (etanercept). Prescribing Information. Immunex. 2011; 4. Remicade® (infliximab). Prescribing Information. Janssen Biotech, Inc. 2011;

# Tofacitinib is a Novel Inhibitor of JAKs that Modulates Cytokines Important in Pathogenesis of RA




JAK=Janus kinase.

Shuai K, Liu B. *Nat Rev Immunol*. 2003;3(11):900-911; Flanagan ME et al, *J Med Chem* 2010; 53:8468-8484

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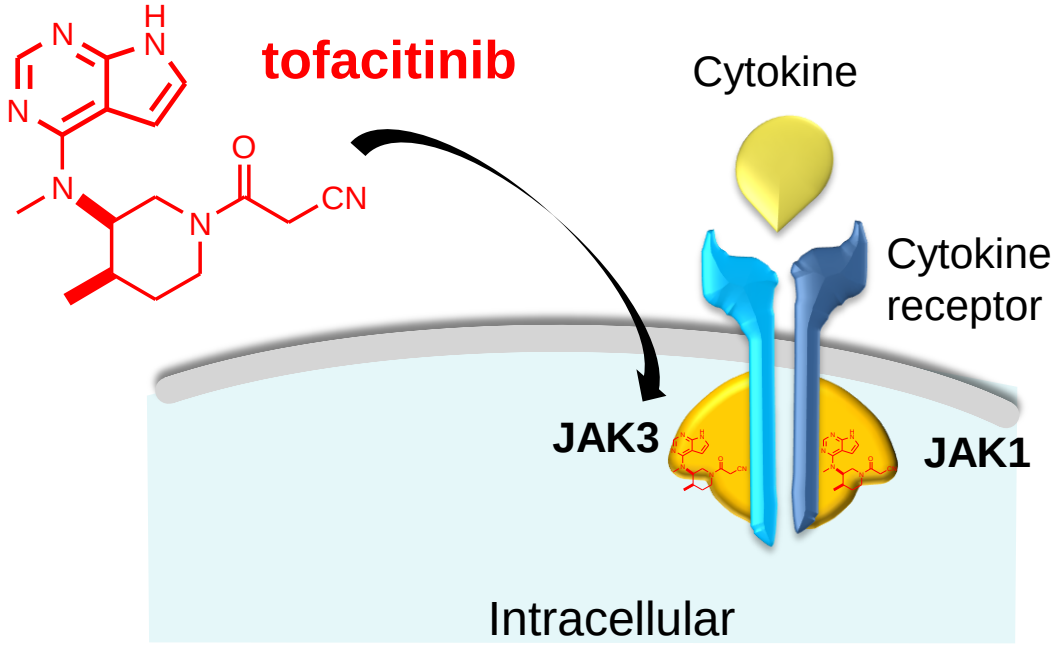
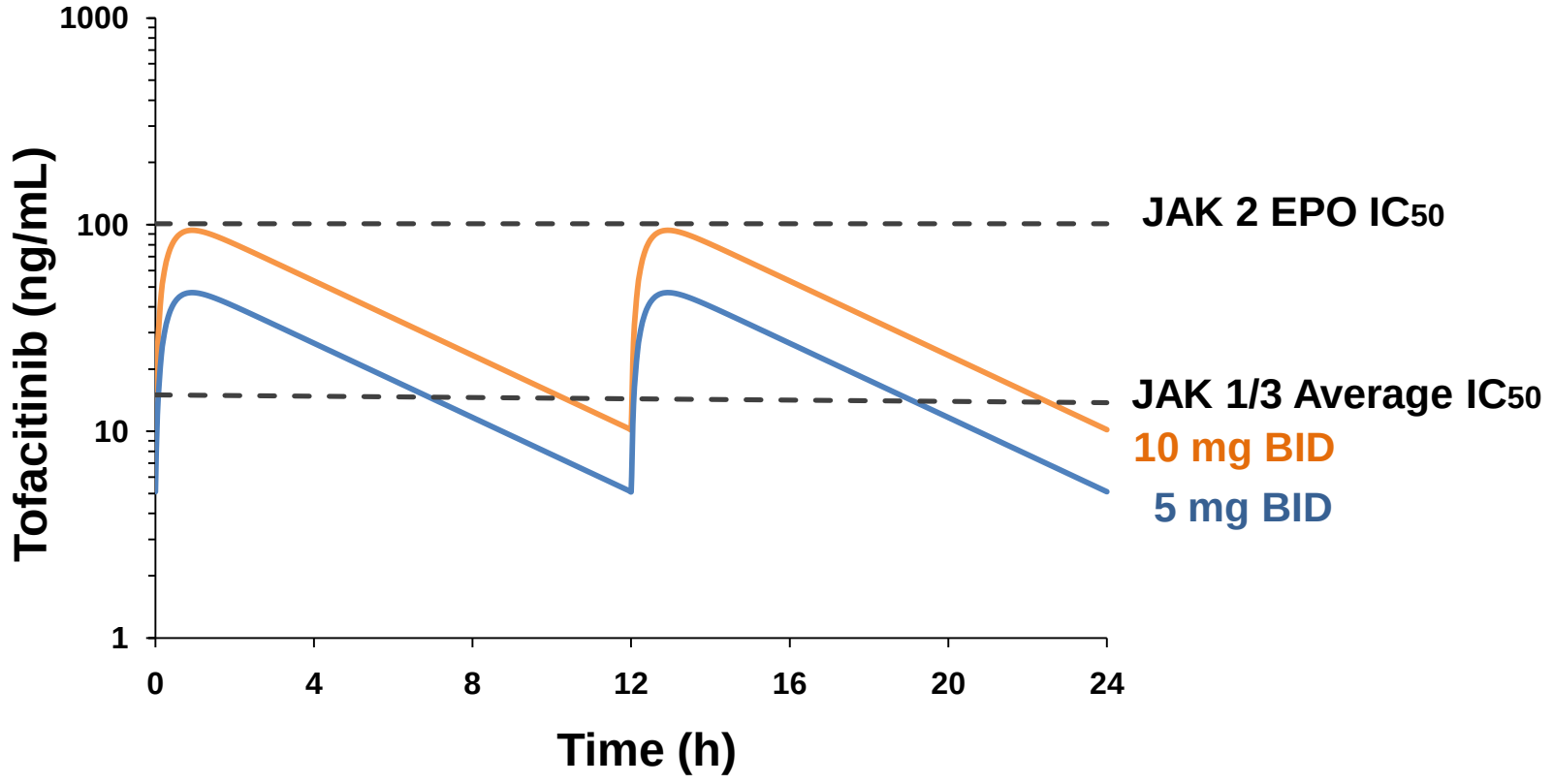



| Key Cytokines in the pathogenesis of RA | |
|---|---|
| **Cytokines** | **JAKs** |
| IL-7 | JAK1/JAK3 |
| IL-15 | JAK1/JAK3 |
| IL-21 | JAK1/JAK3 |
| IL-6 | JAK1/JAK2/Tyk2 |
| IFNα and IFNβ | JAK1/Tyk2 |
| IL-10 | JAK1/Tyk2 |
| IL-12 | JAK2/Tyk2 |
| IL-23 | JAK2/Tyk2 |
| IL-1<br>IL-17<br>IL-18<br>TGF-β<br>TNF | Jak independent |

JAK=Janus kinase.

Shuai K, Liu B. *Nat Rev Immunol*. 2003;3(11):900-911; Flanagan ME et al, *J Med Chem* 2010; 53:8468-8484

# Partial and Reversible Inhibition of JAK with 5 and 10 mg BID



# Tofacitinib Clinical Pharmacology

- Well absorbed
- Dose proportional PK and moderate variability
- Clearance by multiple elimination pathways
  - CYP3A4 (~53%), CYP2C19 (~17%), renal excretion (~30%)
- Potent CYP3A4 inhibitors will increase tofacitinib exposure
- Tofacitinib has a low potential to influence PK of other drugs

# Tofacitinib Proposed Indication and Dosing

- Indicated for:
  - Moderately to severely active rheumatoid arthritis
  - With inadequate response to one or more DMARDs
- May be used as:
  - Monotherapy
  - Coadministered with methotrexate or other nonbiologic DMARDs

# Agenda

| | |
|---|---|
| **Rheumatoid Arthritis: Medical Need** | **Stanley Cohen, M.D.**<br>**Clinical Professor of Rheumatology**<br>**University of Texas Southwestern Medical School, Dallas, TX** |
| **Tofacitinib Efficacy** | **John D. Bradley, M.D.**<br>**Senior Director, Clinical Lead for Tofacitinib RA, Pfizer, Inc.** |
| **Tofacitinib Safety** | **Richard Riese, M.D., Ph.D.**<br>**Senior Director, Clinical Development, Pfizer, Inc.** |
| **Clinician Perspective** | **Stanley Cohen, M.D.**<br>**Clinical Professor of Rheumatology**<br>**University of Texas Southwestern Medical School, Dallas, TX** |
| **Conclusion** | **Yvonne Greenstreet, MB ChB**<br>**Senior Vice President, Medicines Development**<br>**Pfizer, Inc.** |
| **Moderator** | **Samuel H. Zwillich, M.D.**<br>**Senior Director, MDG Lead for Tofacitinib RA, Pfizer, Inc.** |

# Additional Experts

| | |
|---|---|
| **Robert Landewe, M.D.** | **Professor of Rheumatology, Department Internal Medicine/Rheumatology, AmC/UvA Amsterdam** |
| **Vibeke Strand, M.D.** | **Clinical Professor, Division of Immunology/Rheumatology, Stanford University School of Medicine, Stanford, CA** |
| **Philip Schein, M.D.** | **Visiting Professor, University of Oxford, England** |
| **Paul B. Watkins, M.D.** | **Hepatologist, Professor of Medicine, Pharmacy and Public Health Director, Hamner–UNC Institute for Drug Safety Sciences, University of North Carolina, Chapel Hill, NC** |
| **Virgil Brown, M.D.** | **Professor of Medicine Emeritus, Emory University School of Medicine, Atlanta, GA** |

# Rheumatoid Arthritis: Medical Need

Stanley Cohen, M.D.

Clinical Professor, Department of Internal Medicine

University of Texas Southwestern Medical School

Co-Director, Division of Rheumatology, Presbyterian Hospital Dallas

Co-Medical Director, Metroplex Clinical Research Center

Dallas, TX

# Agenda

- Background on rheumatoid arthritis
- Present standards of care
- Limitations of current therapies
- Unmet need for new options

# Rheumatoid Arthritis (RA)

- Chronic, inflammatory, systemic autoimmune disease
- 1.3 million in the United States[1]
- ~70% women[2]
- Age of onset: 40-70 years of age[2]
- Causes significant disability[3]

**1.** *Arthritis Today*. "What is Rheumatoid Arthritis." Accessed 12 April 2011. Available at: http://www.arthritistoday.org/conditions/rheumatoid-arthritis/all-about-ra/what-is-ra.php; 2. Lee D, Weinblatt ,M. *Lancet* 2001;358:903–11; 3. Allaire, S, et al. *Arthritis Care Res* 2008; 59(4): 474-480

# Serious Co-morbidities and Complications of Rheumatoid Arthritis

- **Cardiovascular Disease[1]**
  - Myocardial Infarction
  - Stroke
  - Congestive heart failure
- **Serious infections[2]**
- **Lung cancer[3]**
- **Lymphoma[3]**
- **Premature death[4]**

**Consequences of chronic, uncontrolled, local and systemic inflammation**

1.Naranjo A, et al. *Arthritis Res Ther* 2008;10:R30; 2. Doran MF, et al. *Arthritis Rheum* 2002;46:2287–2293; 3. Smitten AL, et al. *Arthritis Res Ther* 2008;10:R45; 4. Sokka T, et al. *Clin Exp Rheumatol* 2008;26(5 Suppl 51):S35-S61.

# RA Treatment Goals Endorsed by ACR and EULAR[1, 2]

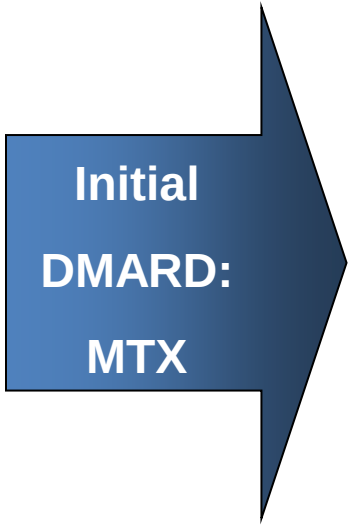
## Rx Goals

- Achieve low disease activity state or remission
- Inhibit progression of structural damage
- Improve physical function and health related quality of life



1. Singh JA, et al. *Arthritis Care Res* 2012;64:625-639; 2. Smolen JS, et al. *Ann Rheum Dis* 2010;69:631-637.

# RA Treatment Paradigm[1, 2]

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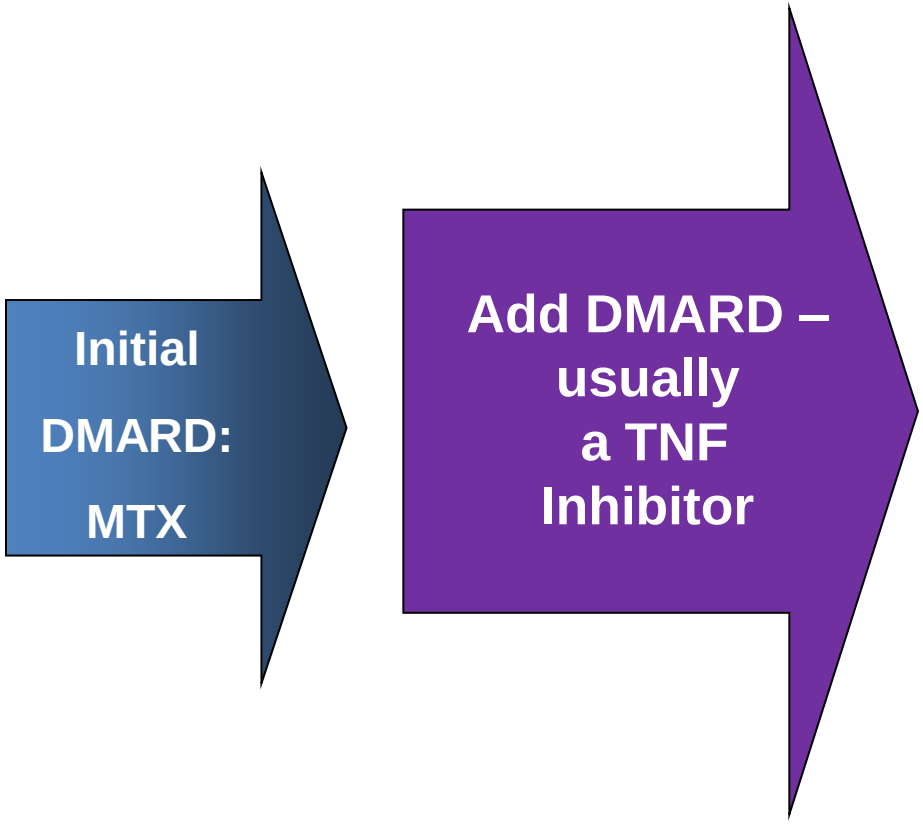


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# Limited Persistence Even on TNF Inhibitors

| | Persistence Rate | |
|---|---|---|
| TNF inhibitor switching status | 12 months (95%CI) | 24 months (95%CI) |
| First TNF inhibitor | 72% (70% to 75%) | 57% (54 to 60%) |
| Second TNF inhibitor | 60% (55% to 64%) | 42% (37% to 47%) |
| Third TNF inhibitor | 63% (54% to 70%) | 42% (33% to 51%) |

Greenberg JD, et al. *Ann Rheum Dis*.2012 Jan 30. [Epub ahead of print].

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# Safety Considerations with DMARDs

- **Serious infections**
  - Bacterial
  - Viral
  - TB/opportunistic
  - PML
- **Immune reactions**
  - Infusion/injection reactions
  - Autoantibodies and drug-induced lupus
  - Demyelination
- **Laboratory changes**
  - Hematologic
  - Transaminase elevations
  - Altered lipid profile
- **Malignancies/lymphoma**
- **Congestive heart failure**

Furst DE, et al. *Ann Rheum Dis.* 2012;71(Supp II):i2-i45. Actemra® (tocilizumab). Prescribing Information. Genentech, Inc. 2011; Cimzia® (certolizumab pegol). Prescribing Information. UCB, Inc. 2011; Enbrel® (etanercept). Prescribing Information. Immunex. 2011; Humira® (adalimumab). Prescribing Information. Abbott Laboratories. 2011; Kineret® (anakinra). Prescribing Information. Biovitrum AB. 2009; Orencia® (abatacept). Prescribing Information. Bristol-Myers Squibb. 2011; Remicade® (infliximab). Prescribing Information. Janssen Biotech, Inc. 2011; Rituxan® (rituximab). Prescribing Information. Biogen Idec Inc. and Genentech, Inc. 2012; Simponi® (golimumab). Prescribing Information. Janssen Biotech, Inc. 2011.

# Unmet Medical Need in RA

- **Patients need multiple therapies to maintain efficacy and positive benefit:risk over time**
  - Oral option would be welcome
- **Research goal:**
  - Novel, small molecular therapies
  - Oral administration
  - Efficacy and safety similar to parenteral biologic DMARDs
- **Many candidates have failed in clinical trials**

***GOAL: Oral DMARD/acceptable benefit:risk***

# Efficacy

**John D. Bradley, M.D.**

**Senior Director and Clinical Lead for Tofacitinib RA Program**

**Pfizer, Inc.**

# Agenda

- Phase 2
  - Dose response
- Phase 3 Study Overview
- Tofacitinib Phase 3 Efficacy Data
- Additional Efficacy Data
  - Patient-Reported Outcomes
  - Tofacitinib in subpopulations
  - Maintenance of efficacy
- Conclusion

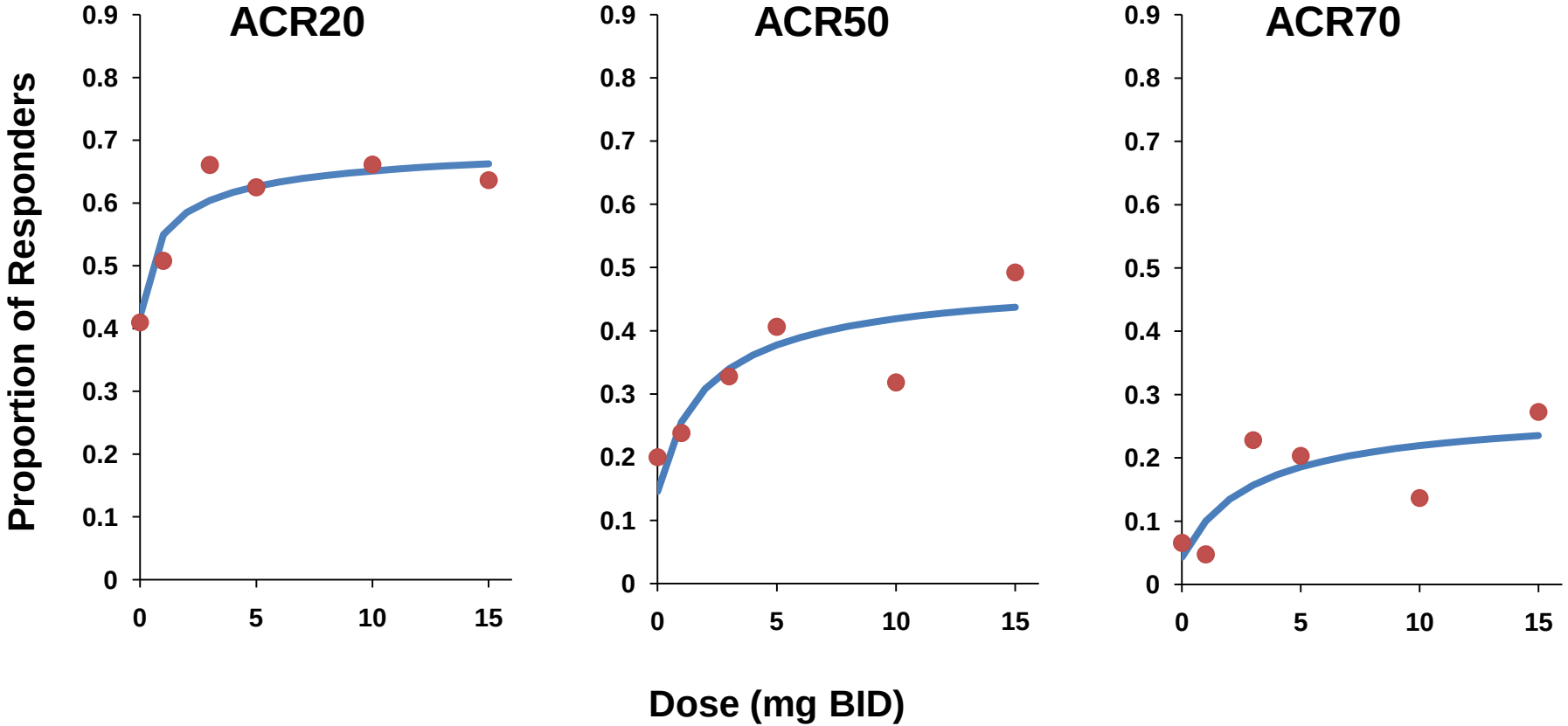
# American College of Rheumatology (ACR) Response Criteria

- Composite endpoint with 7 components
- Proportion of patients achieving a target % improvement from baseline (20, 50, 70). For ACR20:
- At least a 20% reduction in swollen and tender/painful joints
- At least a 20% reduction in at least 3 of the 5 remaining criteria, including:
  - Patient global assessment of arthritis
  - Patient assessment of arthritis pain
  - Patient disability/functional assessment
  - Physician global assessment of arthritis
  - Laboratory test for inflammation

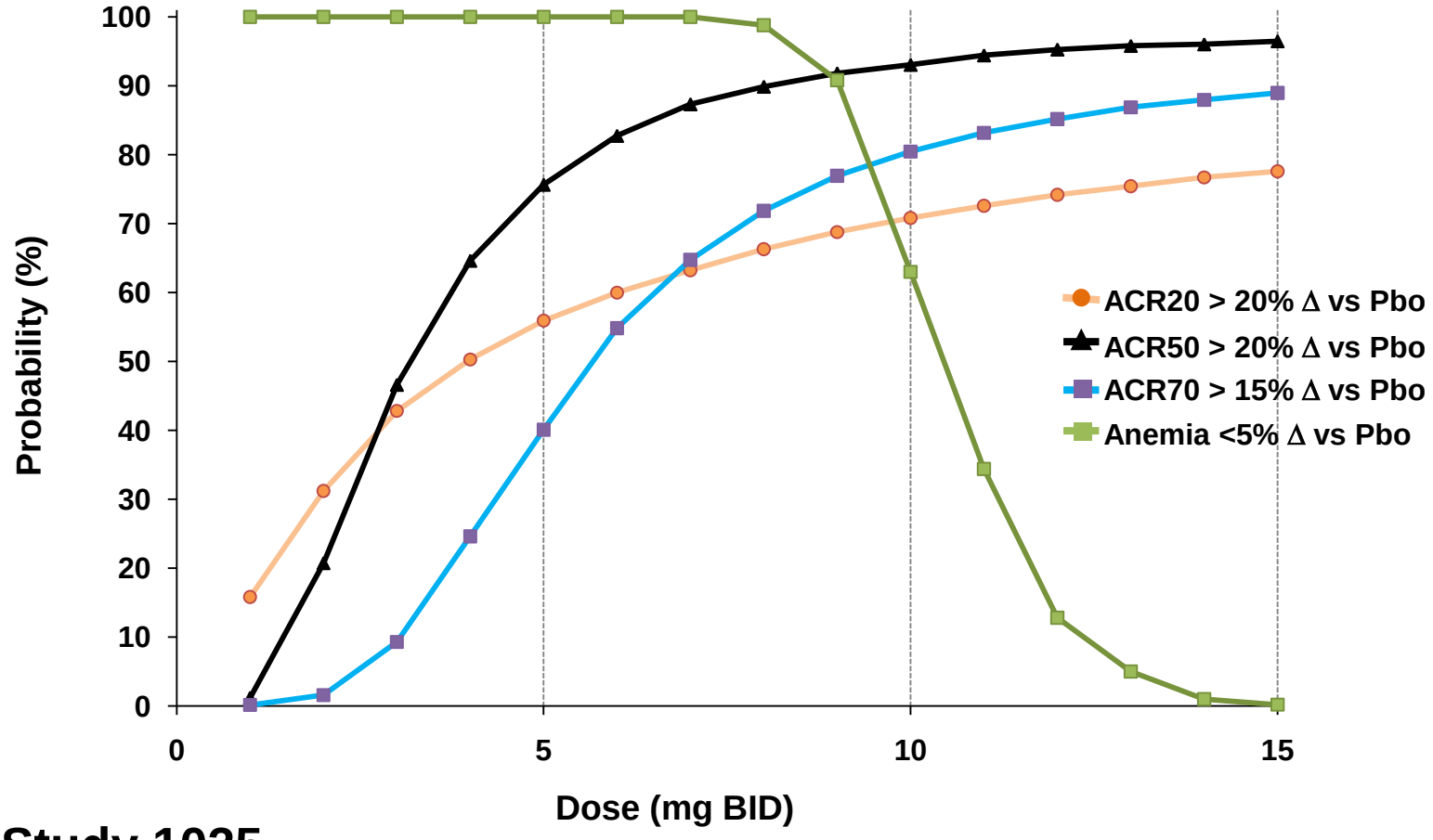
# Phase 2 Program Evaluated a Wide Range of Tofacitinib Doses

- Phase 2 Program
  - 5 placebo-controlled randomized studies
  - Tofacitinib as monotherapy and in combination with background methotrexate (MTX)
  - 1617 patients
  - Dose range: 1-30 mg twice daily
  - Treatment duration up to 6 months

# ACR Dose Response (Observed and Predicted) Study 1025 – Month 3

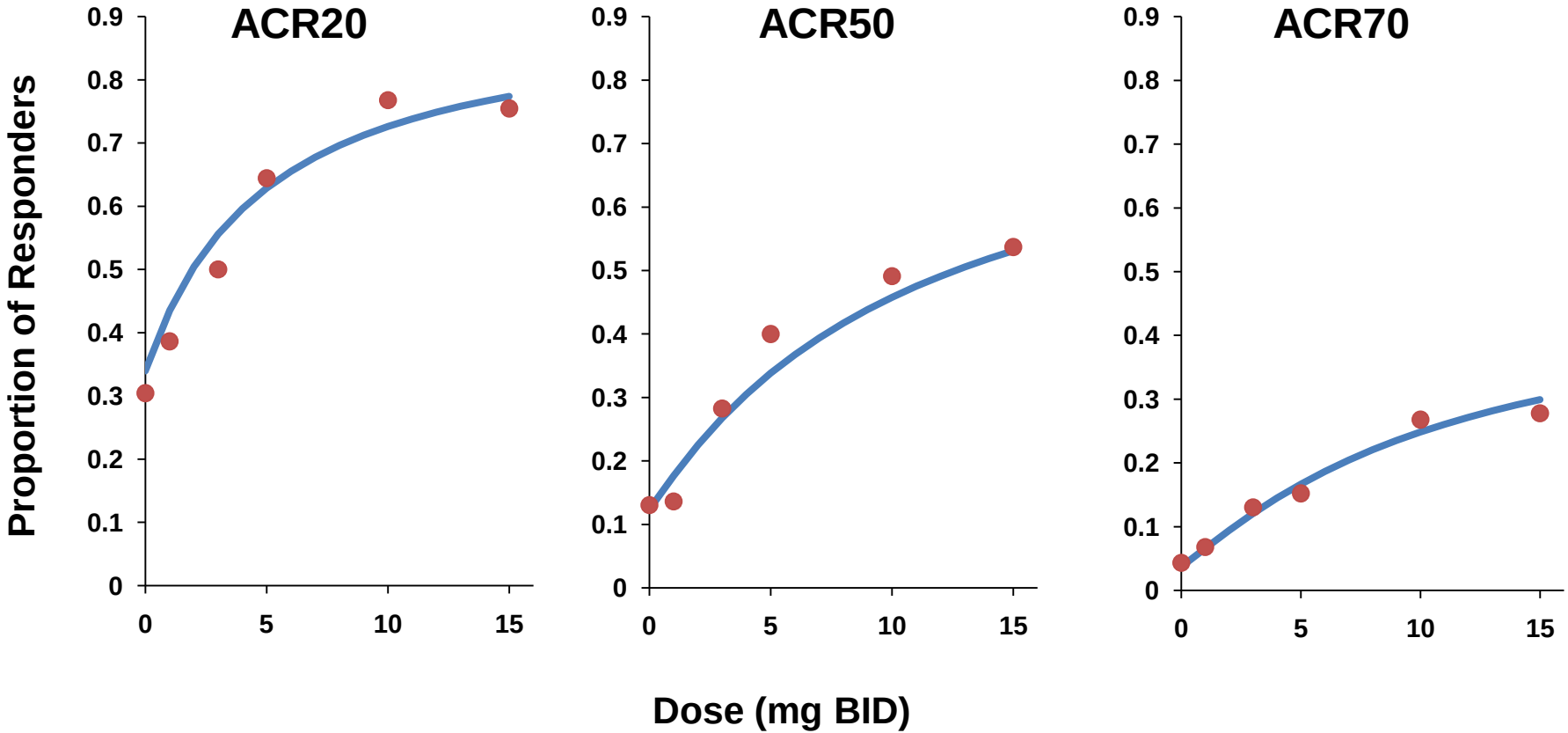


# Dose Selection Rationale for Phase 3 Studies




Based on Study 1025

# ACR Dose Response (Observed and Predicted) Study 1035 – Month 3



# Agenda

- Phase 2
- Phase 3 Study Overview
- Tofacitinib Phase 3 Efficacy Data
- Additional Efficacy Data
  - Patient-Reported Outcomes
  - Tofacitinib in subpopulations
  - Maintenance of efficacy, including long-term open-label extension studies
- Conclusion

# Global Phase 3 Program: 5 Randomized Studies in DMARD Inadequate Responders

Tofacitinib efficacy and safety evaluated in treatment settings representative of clinical practice

- In patients who have had an inadequate response to non-biologic DMARDs
  - In combination with non-biologic DMARDs
  - As monotherapy
- In patients who have had an inadequate response (IR) to biologic DMARDs, particularly tumor necrosis factor (TNF) inhibitors

# Phase 3 Study Designs

| Duration ≥ 1 year | | | |
|---|---|---|---|
| **Study N** | **Study 1044 N=797** | **Study 1046 N=792** | **Study 1064 N=717** |
| **Population** | **MTX IR** | **DMARD IR** | **MTX IR** |
| **Background Treatment** | **MTX** | **DMARDs** | **MTX** |

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| **Background Treatment** | **MTX** | **DMARDs** | **MTX** |
| **Distinguishing Feature** | **X-Ray** | | |

**“Scan”**

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**“Scan”** **“Sync”**

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| **Background Treatment** | **MTX** | **DMARDs** | **MTX** |
| **Distinguishing Feature** | **X-Ray** | **Background DMARDs** | **Active Control (adalimumab)** |
| | ⬇ | ⬇ | ⬇ |
| | **“Scan”** | **“Sync”** | **“Standard”** |

# Phase 3 Study Designs

| | Duration ≥ 1 year | | | Duration of 6 Months |
|---|---|---|---|---|
| **Study N** | **Study 1044 N=797** | **Study 1046 N=792** | **Study 1064 N=717** | **Study 1032 N=399** |
| **Population** | MTX IR | DMARD IR | MTX IR | TNF IR |
| **Background Treatment** | MTX | DMARDs | MTX | MTX |
| **Distinguishing Feature** | X-Ray | Background DMARDs | Active Control (adalimumab) | |
| | ⬇ | ⬇ | ⬇ | |
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| | ⬇ | ⬇ | ⬇ | ⬇ |
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| | Duration ≥ 1 year | | | Duration of 6 Months | |
|---|---|---|---|---|---|
| **Study N** | **Study 1044 N=797** | **Study 1046 N=792** | **Study 1064 N=717** | **Study 1032 N=399** | **Study 1045 N=610** |
| **Population** | MTX IR | DMARD IR | MTX IR | TNF IR | DMARD IR |
| **Background Treatment** | MTX | DMARDs | MTX | MTX | None |
| **Distinguishing Feature** | X-Ray | Background DMARDs | Active Control (adalimumab) | TNF Failures | |
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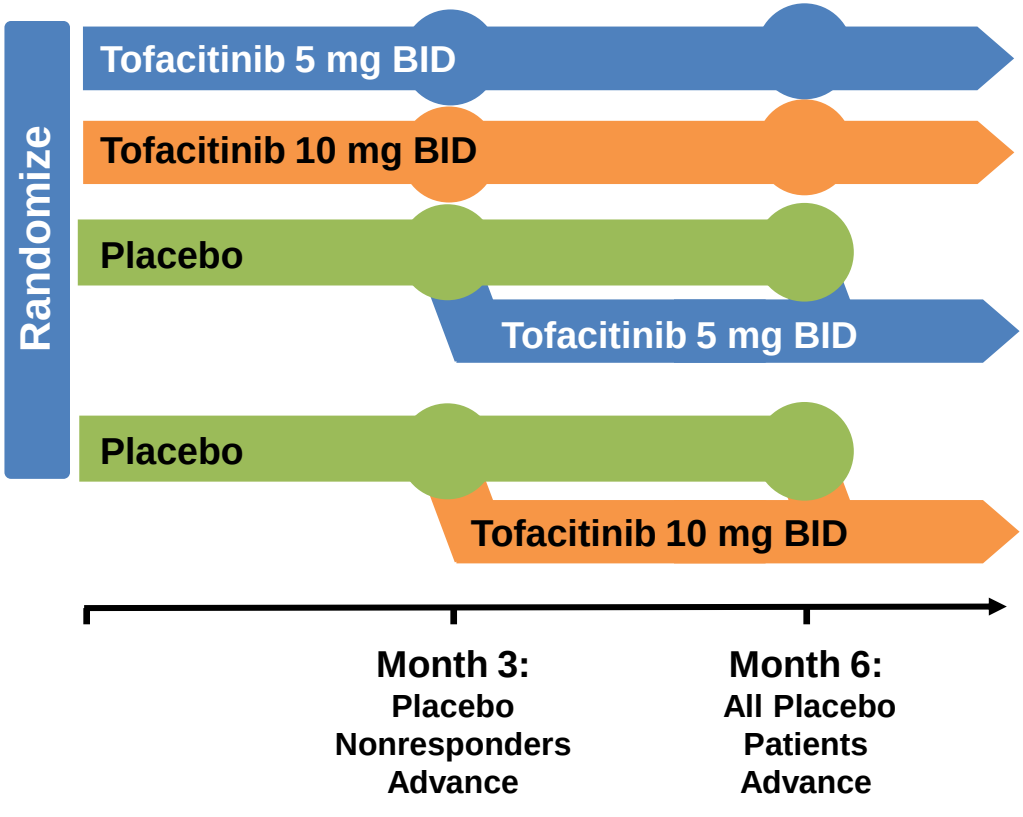
| **Background Treatment** | MTX | DMARDs | MTX | MTX | None |
| **Distinguishing Feature** | X-Ray | Background DMARDs | Active Control (adalimumab) | TNF Failures | Monotherapy |
| | ⬇ | ⬇ | ⬇ | ⬇ | ⬇ |
| | **“Scan”** | **“Sync”** | **“Standard”** | **“Step”** | **“Solo”** |

# Phase 3 Study Treatment Assignments

- Tofacitinib added to background DMARDs, mostly MTX, in Scan/1044, Sync/1046, Standard/1064 and Step/1032
- Tofacitinib administered as monotherapy in Solo/1045
- Placebo treatment limited to minimize risk of inadequate treatment

# Phase 3 Studies of 1-2 Years Duration
## Placebo Treatment Duration Depended on Response

- DMARD IR
- Continued background DMARD treatment
  - **Scan/1044**: 2 Year x-ray on background MTX
  - **Sync/1046**: 1 Year background DMARD
  - **Standard/1064**: 1 year background MTX with adalimumab active control



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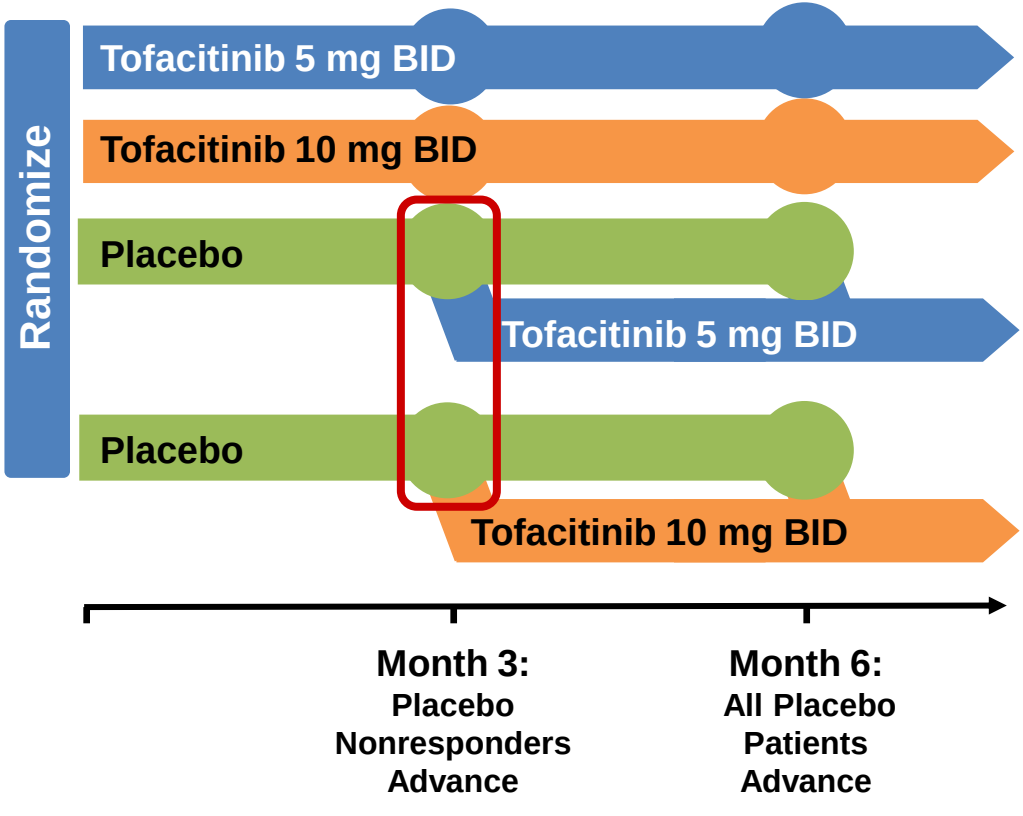

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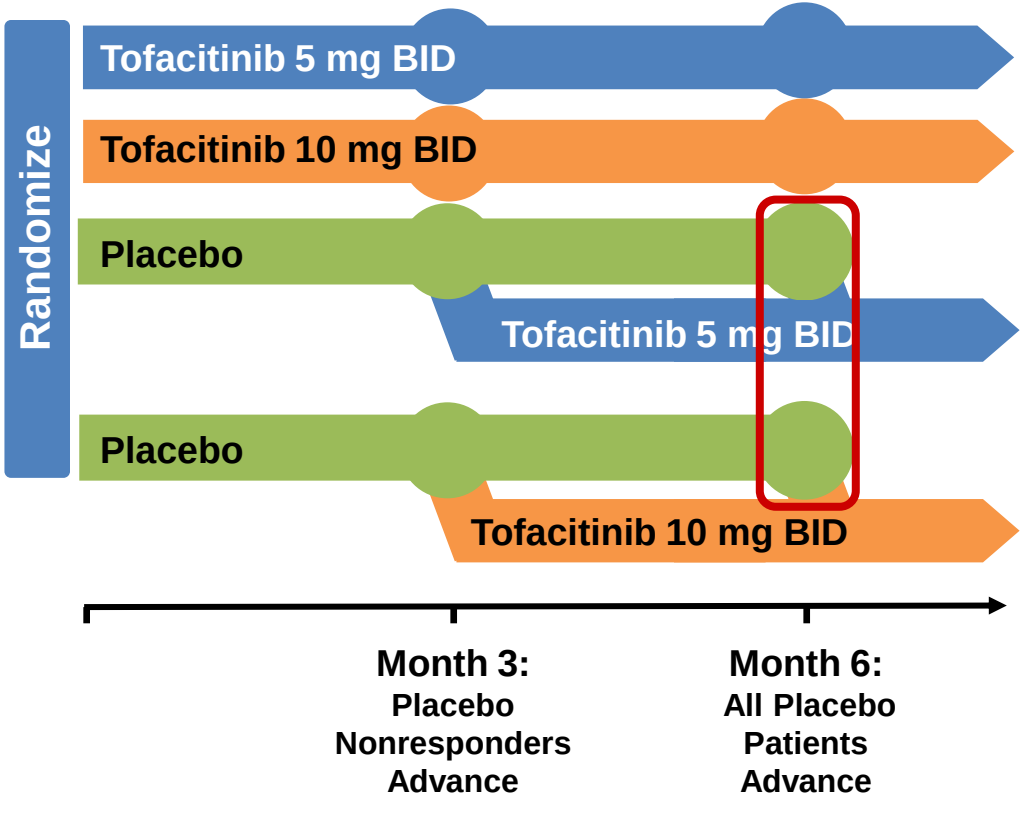
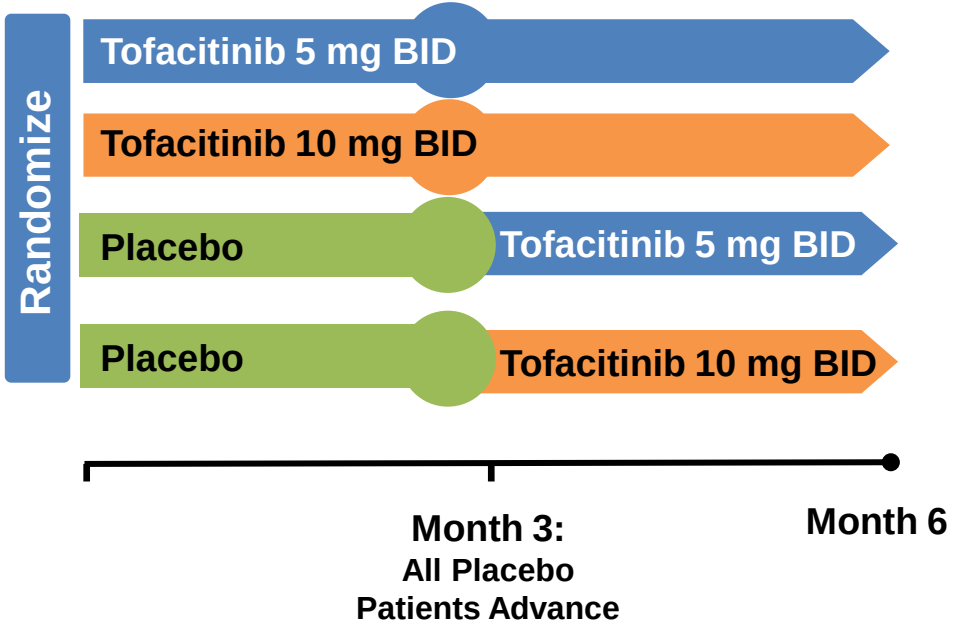


# Phase 3 Studies of Six Month Duration
## Placebo Treatment Limited to 3 Months

- **Step/1032**: TNF IR on background MTX
- **Solo/1045**: Monotherapy study in DMARD IR



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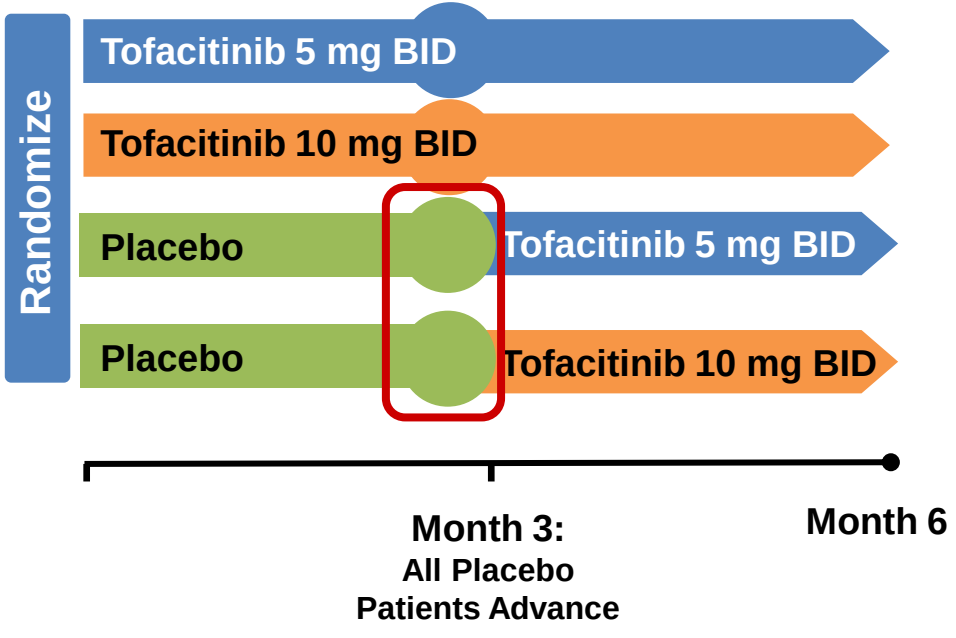


# Four Primary Efficacy Endpoints

- Primary efficacy endpoints (vs placebo)
  - ACR20 response rate
  - Change from baseline in Health Assessment Questionnaire – Disability Index, HAQ-DI
  - Percentage achieving DAS28-4(ESR)<2.6
  - Change from baseline in van der Heijde modified Total Sharp Score, mTSS (Scan Study only)

DAS, Disease Activity Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde modified total Sharp score

# Primary Endpoints Evaluated with Step-Down Procedure to Control for Type 1 Error

- Order of analyses (in Sync, Standard, Step, Solo, Scan)
  1. ACR20 response rate
  2. Change in mTSS (Scan only)
  3. Change from baseline in HAQ-DI
  4. Percentage achieving DAS28<2.6
- Statistical significance ($p \leq 0.05$) is tested for 10 mg, followed by 5 mg
- After ACR20, significance is claimed only if the current *and* prior endpoint are significant for the treatment

# Phase 3 Studies: Primary Analysis Timepoints

| | Scan/ 1044 N=797 | Sync/ 1046 N=792 | Standard/ 1064 N=717 | Step/ 1032 N=399 | Solo/ 1045 N=610 |
|---|---|---|---|---|---|
| **Primary Endpoints (Months)** | | | | | |
| ACR 20 | 6 | 6 | 6 | 3 | 3 |
| mTSS | 6 | NA | NA | NA | NA |
| HAQ-DI | 3 | 3 | 3 | 3 | 3 |
| DAS28<2.6 | 6 | 6 | 6 | 3 | 3 |

# Phase 3 Studies: Primary Analysis Timepoints

| | Scan/ 1044 N=797 | Sync/ 1046 N=792 | Standard/ 1064 N=717 | Step/ 1032 N=399 | Solo/ 1045 N=610 |
|---|---|---|---|---|---|
| **Primary Endpoints (Months)** | | | | | |
| ACR 20 | 6 | 6 | 6 | 3 | 3 |
| mTSS | 6 | NA | NA | NA | NA |
| HAQ-DI | 3 | 3 | 3 | 3 | 3 |
| DAS28<2.6 | 6 | 6 | 6 | 3 | 3 |

# Patient Geographic Region of Origin in the Phase 3 Studies

| Geographic Region (%) | Scan/ 1044 N=797 | Sync/ 1046 N=792 | Standard/ 1064 N=717 | Step/ 1032 N=399 | Solo/ 1045 N=610 |
|---|---|---|---|---|---|
| United States | 16.9 | 17.4 | 14.5 | 41.6 | 24.9 |
| European Union | 23.7 | 25.4 | 55.8 | 46.1 | 33.9 |
| Latin America | 14.4 | 13.7 | 11.9 | 5.3 | 27.2 |
| ROW | 45.0 | 43.5 | 17.8 | 7.0 | 14.0 |

# Baseline Characteristics in the Phase 3 Studies

| | Scan/ 1044 N=797 | Sync/ 1046 N=792 | Standard/ 1064 N=717 | Step/ 1032 N=399 | Solo/ 1045 N=610 |
|---|---|---|---|---|---|
| Female (%) | 85 | 81 | 82 | 84 | 87 |
| Age, mean (years) | 53 | 52 | 53 | 55 | 52 |
| Duration of RA (years) | 9.0 | 8.9 | 7.7 | 12.3 | 8.2 |
| RF positive (%) | 76.6 | 73.2 | 67.0 | 62.7 | 65.0 |
| TJC (68) | 23.4 | 25.5 | 27.1 | 28.0 | 29.2 |
| SJC (66) | 14.3 | 14.4 | 16.3 | 16.6 | 16.8 |
| CRP, mg/L, mean | 15.7 | 17.5 | 16.5 | 17.2 | 20.2 |
| HAQ-DI (0-3), mean | 1.38 | 1.42 | 1.49 | 1.58 | 1.52 |
| DAS28-4(ESR), mean | 6.29 | 6.31 | 6.46 | 6.44 | 6.69 |

RF, rheumatoid factor

# Prior DMARD Treatment in the Phase 3 Studies

| % of Patients | Scan/ 1044 N=797 | Sync/ 1046 N=792 | Standard/ 1064 N=717 | Step/ 1032 N= 399 | Solo/ 1045 N=610 |
|---|---|---|---|---|---|
| Methotrexate | 99.9 | 84.3 | 100 | 99.5† | 84.9 |
| Anti-malarials | 40.8 | 22.1 | 36.3 | 14.0 | 48.0 |
| Leflunomide | 17.1 | 29.9 | 16.7 | 17.5 | 22.6 |
| Sulfasalazine | 28.6 | 20.8 | 28.7 | 10.5 | 24.3 |
| Any TNF Inhibitor | 15.9 | 6.6 | 7.1 | 99.2 | 16.2 |
| Other Biologic DMARDs | 4.6 | 2.9 | 2.1 | 11.5 | 6.7 |
| Oral Corticosteroids | 61.5 | 54.3 | 62.8 | 59.9 | 58.5 |

† Prior MTX usages were not recorded for 2 patients in error.

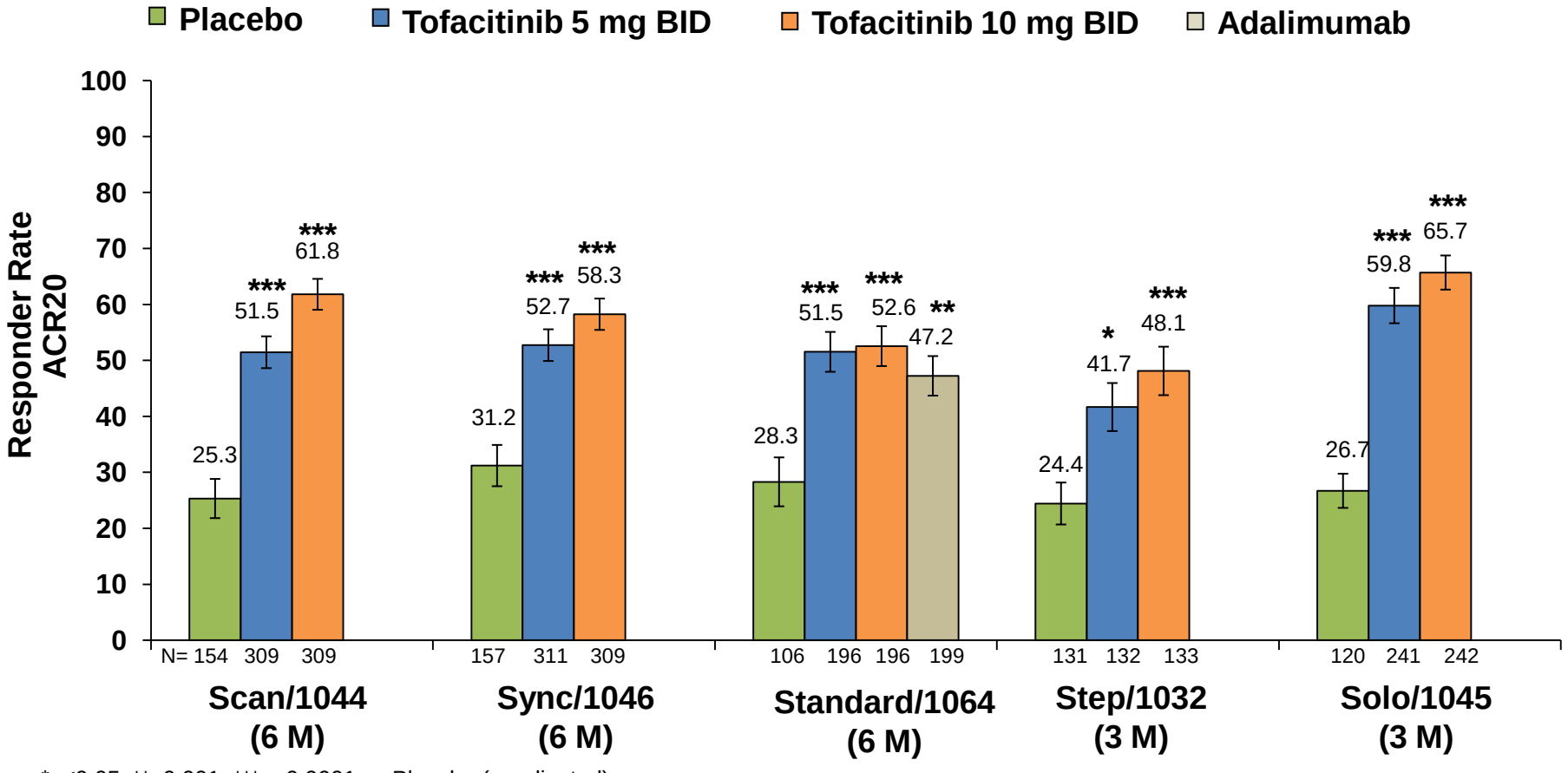
# Patient Disposition in Phase 3 Studies

- Completion rates by treatment group were consistent within studies
- Discontinuations due to adverse events were similar between tofacitinib doses and adalimumab
  - Placebo treatment had fewer adverse event-associated discontinuations
- Discontinuations due to lack of efficacy were more frequent in placebo groups

# Agenda

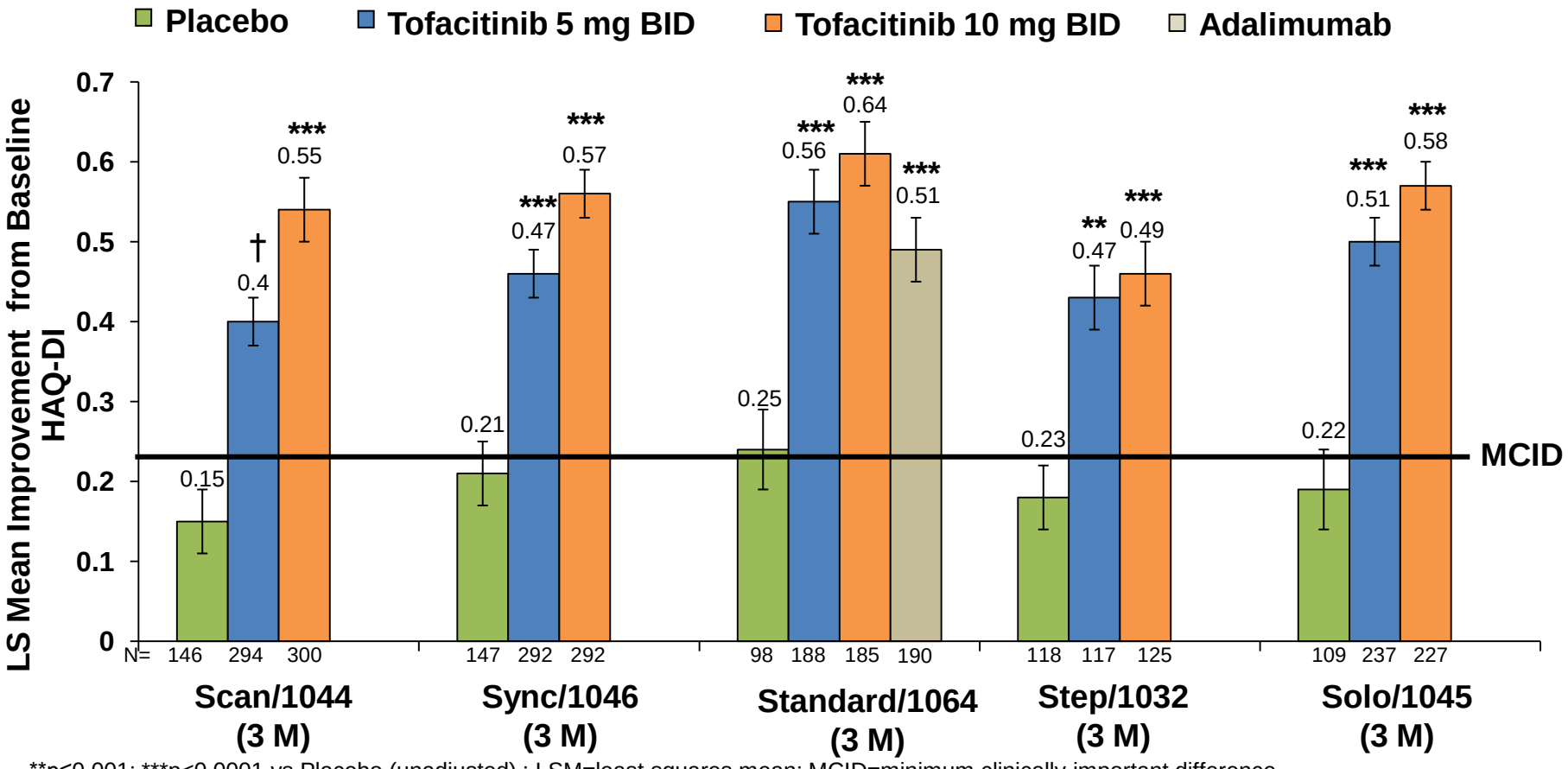
- Phase 2
- Phase 3 Study Overview
- Tofacitinib Phase 3 Efficacy Data
- Additional Efficacy Data
  - Patient-Reported Outcomes
  - Tofacitinib in subpopulations
  - Maintenance of efficacy, including long-term open-label extension studies
- Conclusion

# Consistent ACR20 Response Across Studies




*p≤0.05; **p0.001; ***p<0.0001 vs Placebo (unadjusted)

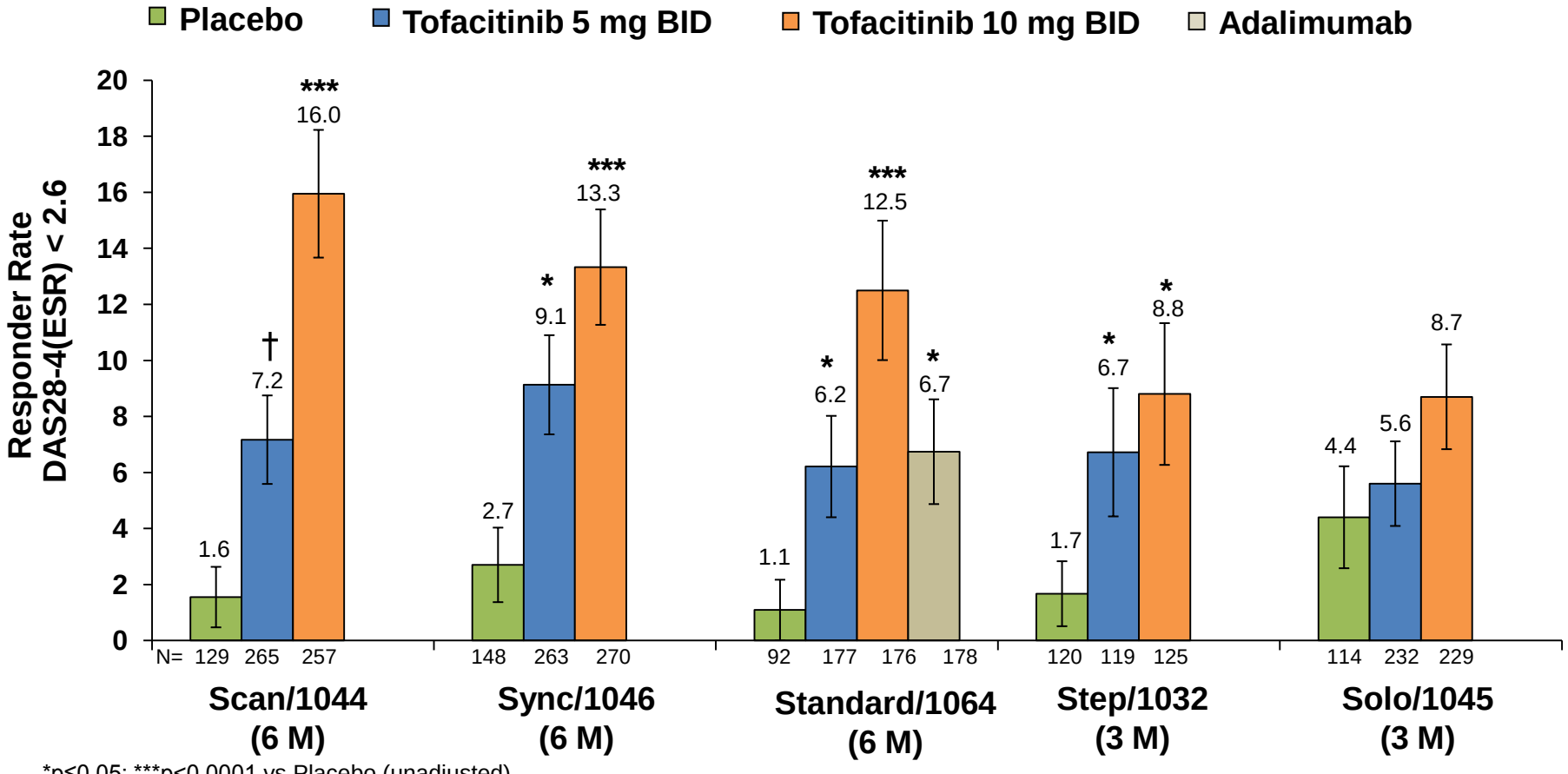
# Consistent HAQ-DI Response Across Studies




**p≤0.001; ***p<0.0001 vs Placebo (unadjusted) ; LSM=least squares mean; MCID=minimum clinically important difference.

†Statistical significance could not be declared in the Scan study due to the step down procedure

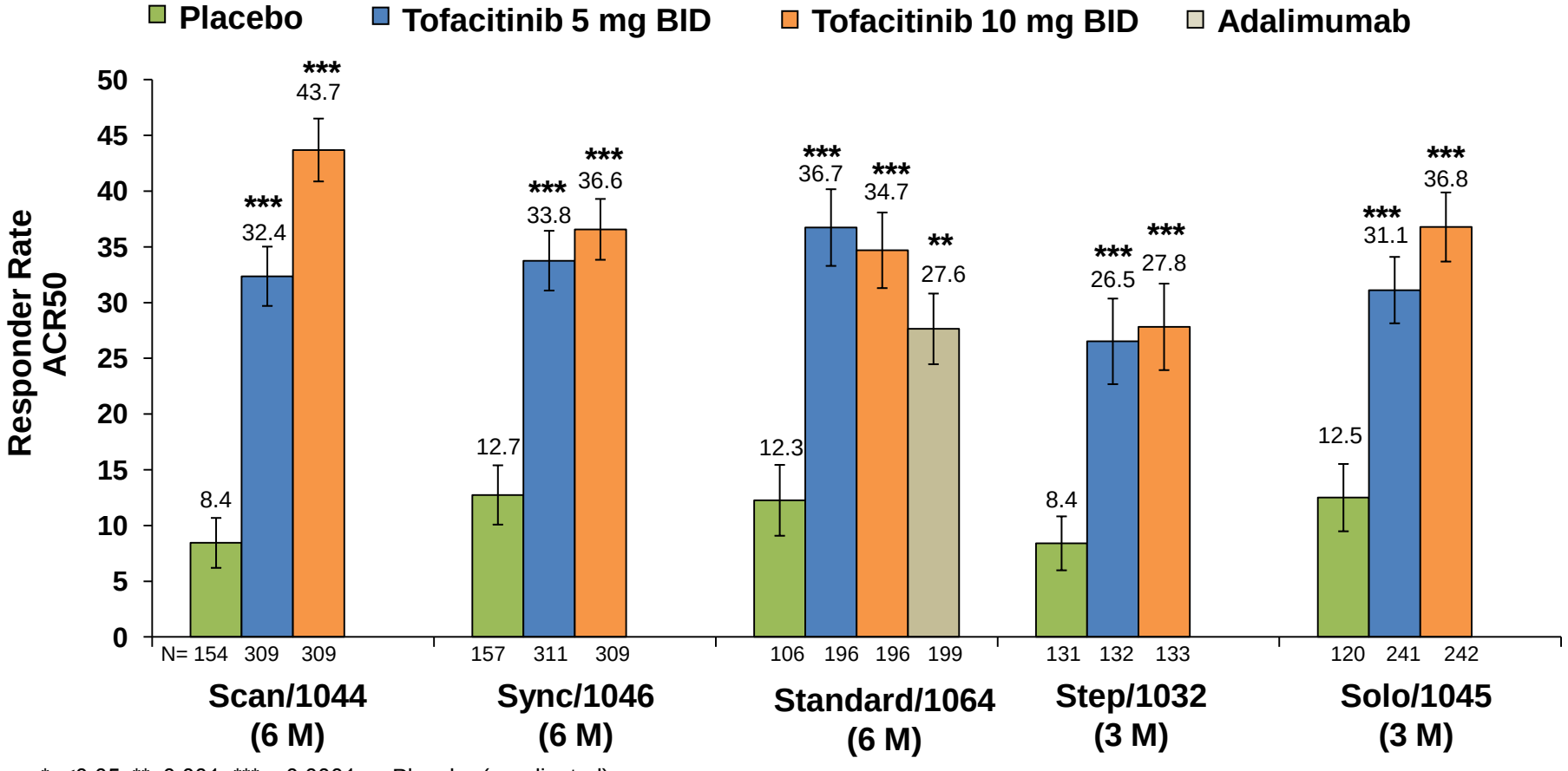
# Consistent DAS28 <2.6 Response Across Studies




*p≤0.05; ***p<0.0001 vs Placebo (unadjusted)

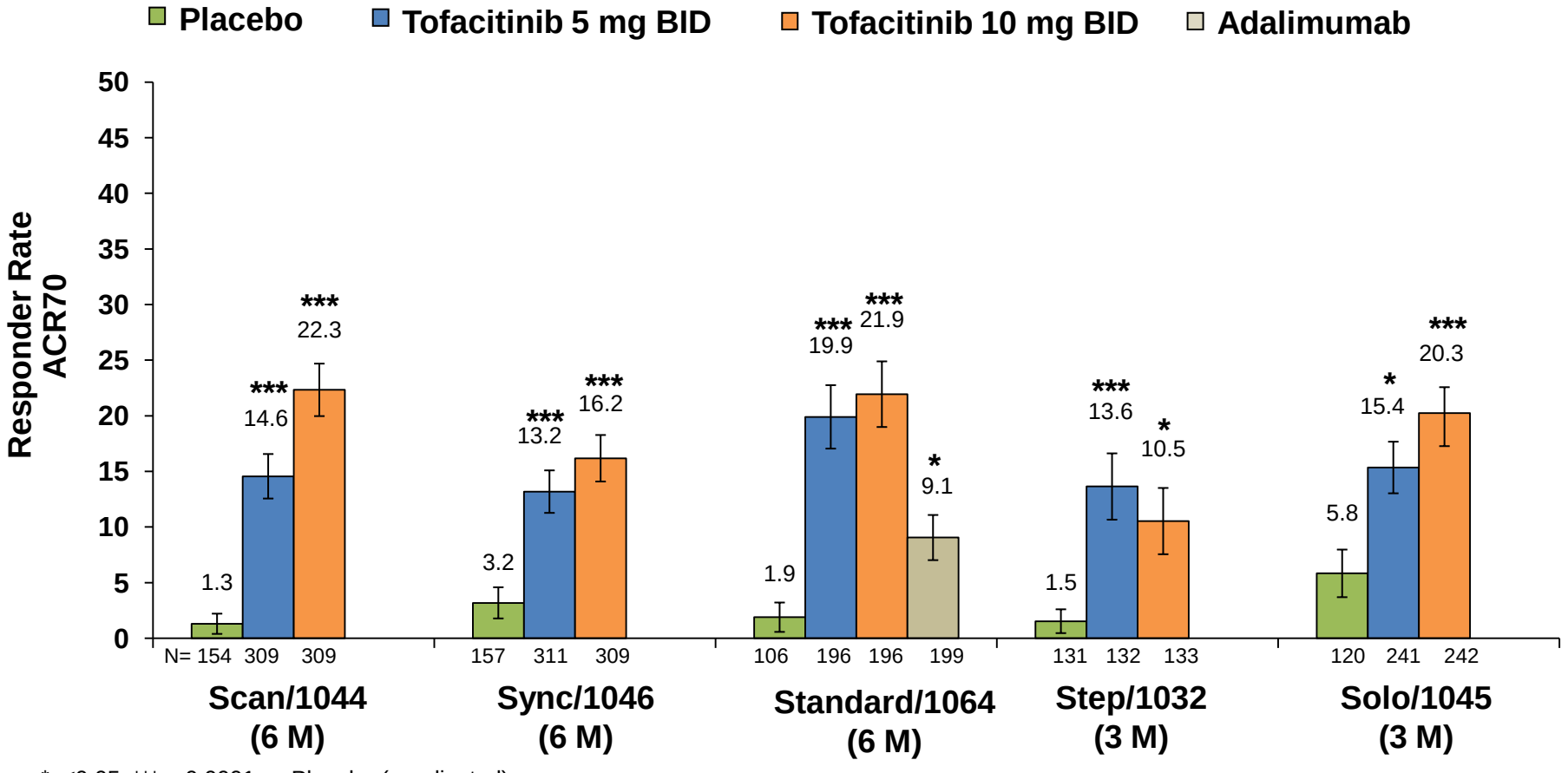
†Statistical significance could not be declared in the Scan study due to the step down procedure

# Consistent ACR50 Response Across Studies



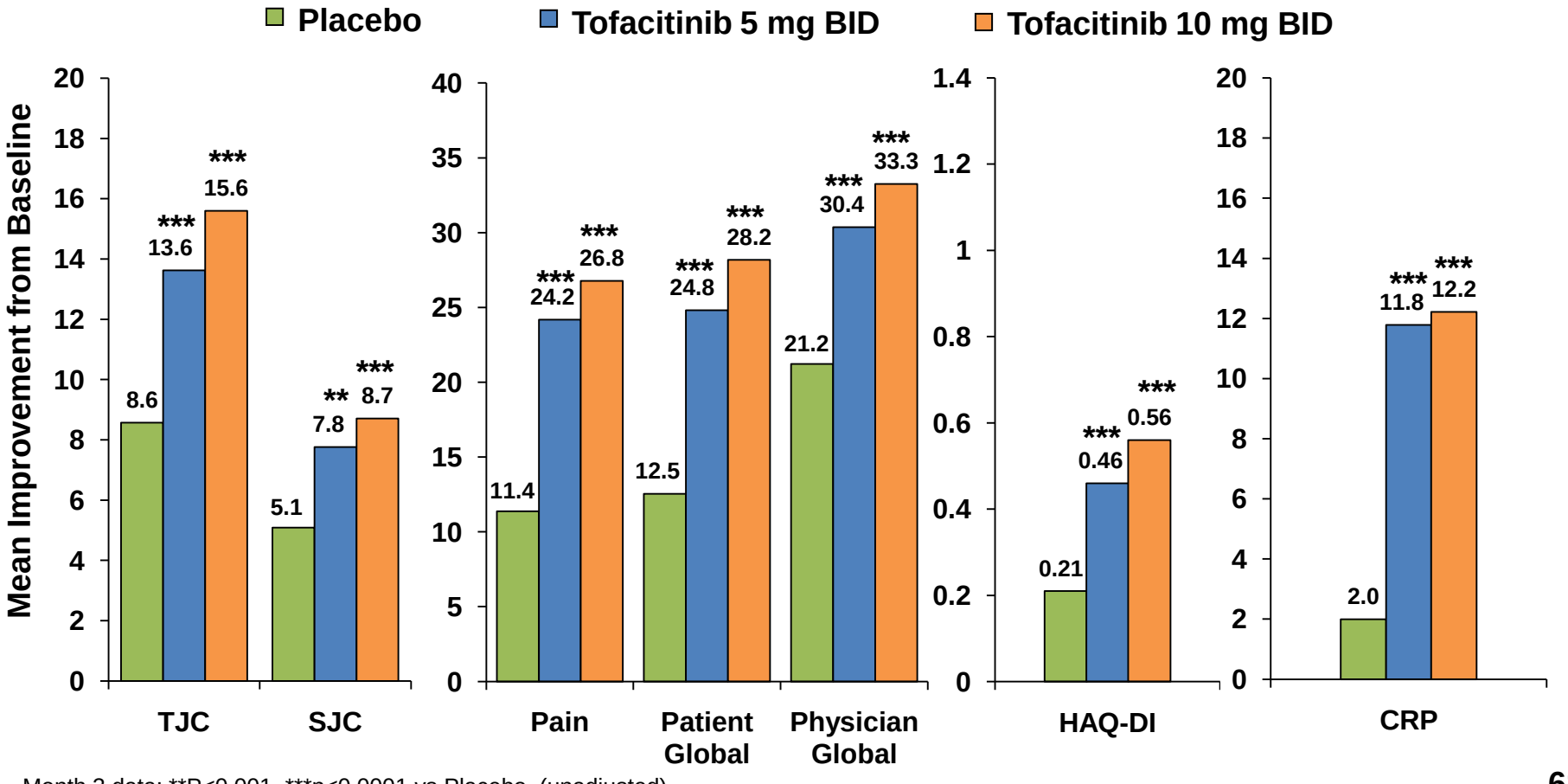

*p≤0.05; **p0.001; ***p<0.0001 vs Placebo (unadjusted)

# Consistent ACR70 Response Across Studies



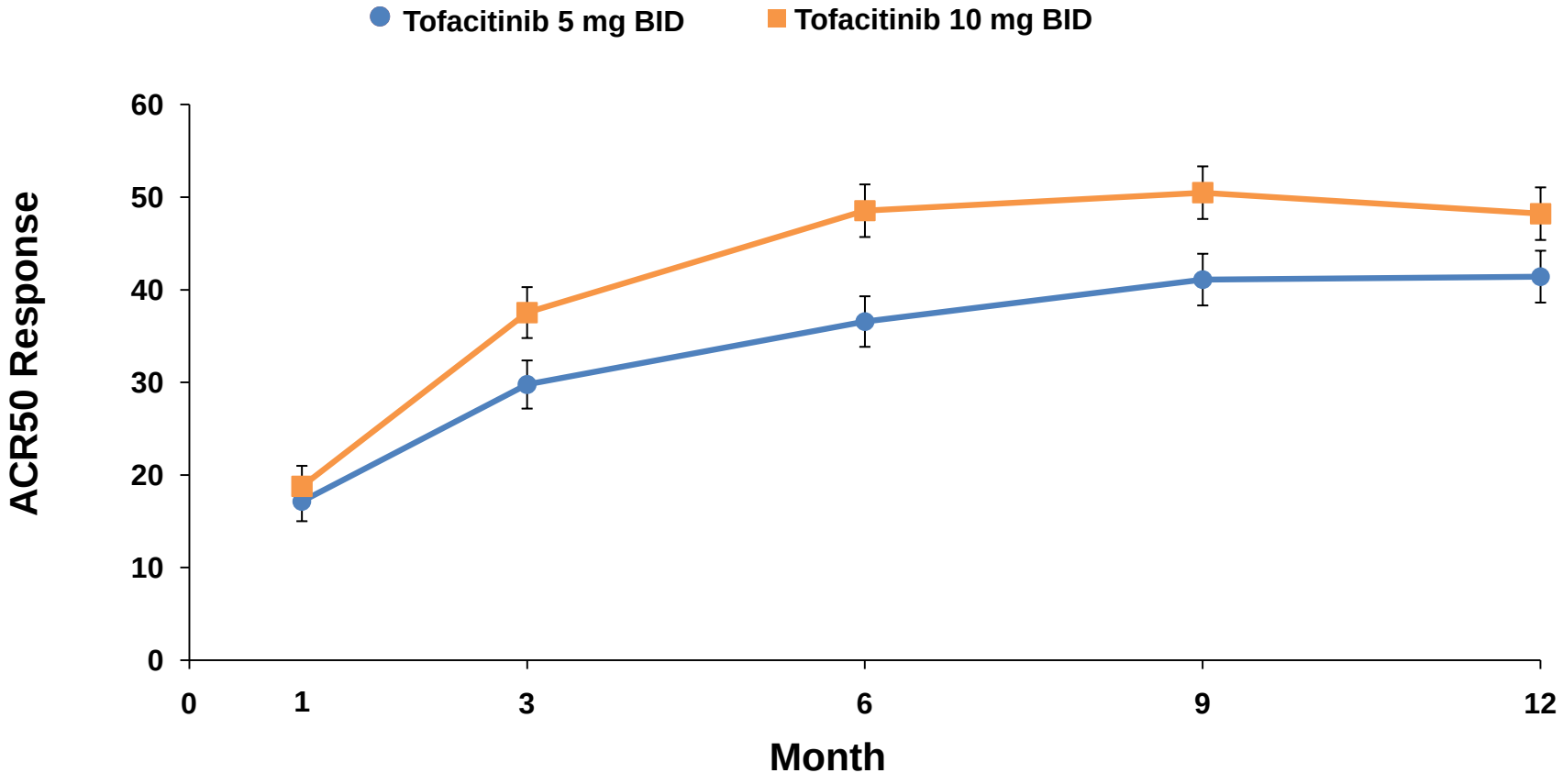

*p≤0.05; ***p<0.0001 vs Placebo (unadjusted)

# Improvements Across All ACR Response Components Sync/1046 Study



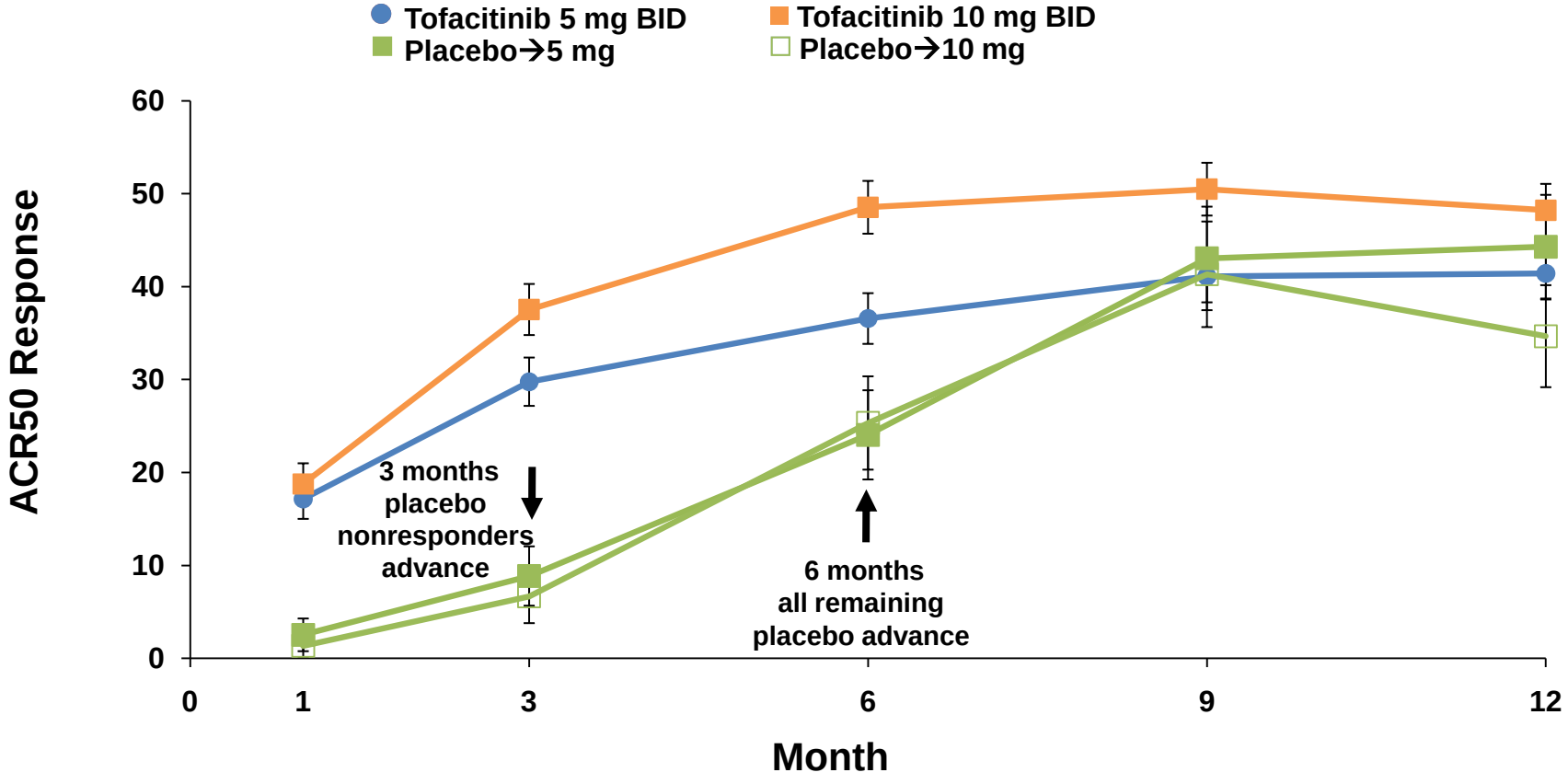

Month 3 data: **P<0.001, ***p<0.0001 vs Placebo (unadjusted)

# ACR50 Responses Maintained: Scan/1044 Study



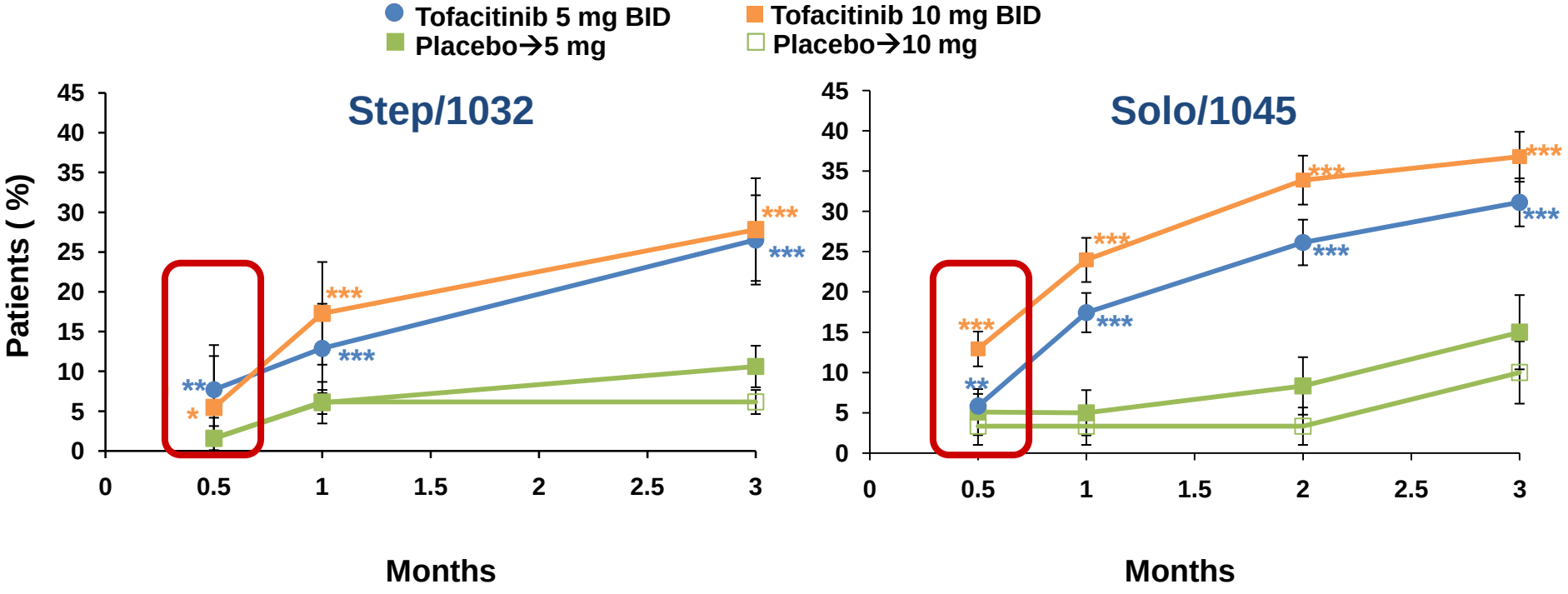

Modified intention-to-treat, last-observation-carried-forward

# ACR50 Responses Maintained: Scan/1044 Study




Modified intention-to-treat, last-observation-carried-forward

# ACR50 Response as Early as Two Weeks




ACR50; For secondary endpoints no multiple-comparisons correction was applied to p-values; and statistical significance was defined as *p≤0.05; **p<0.001; ***p<0.0001 vs baseline
FAS, full analysis set; NRI, non-responder imputation

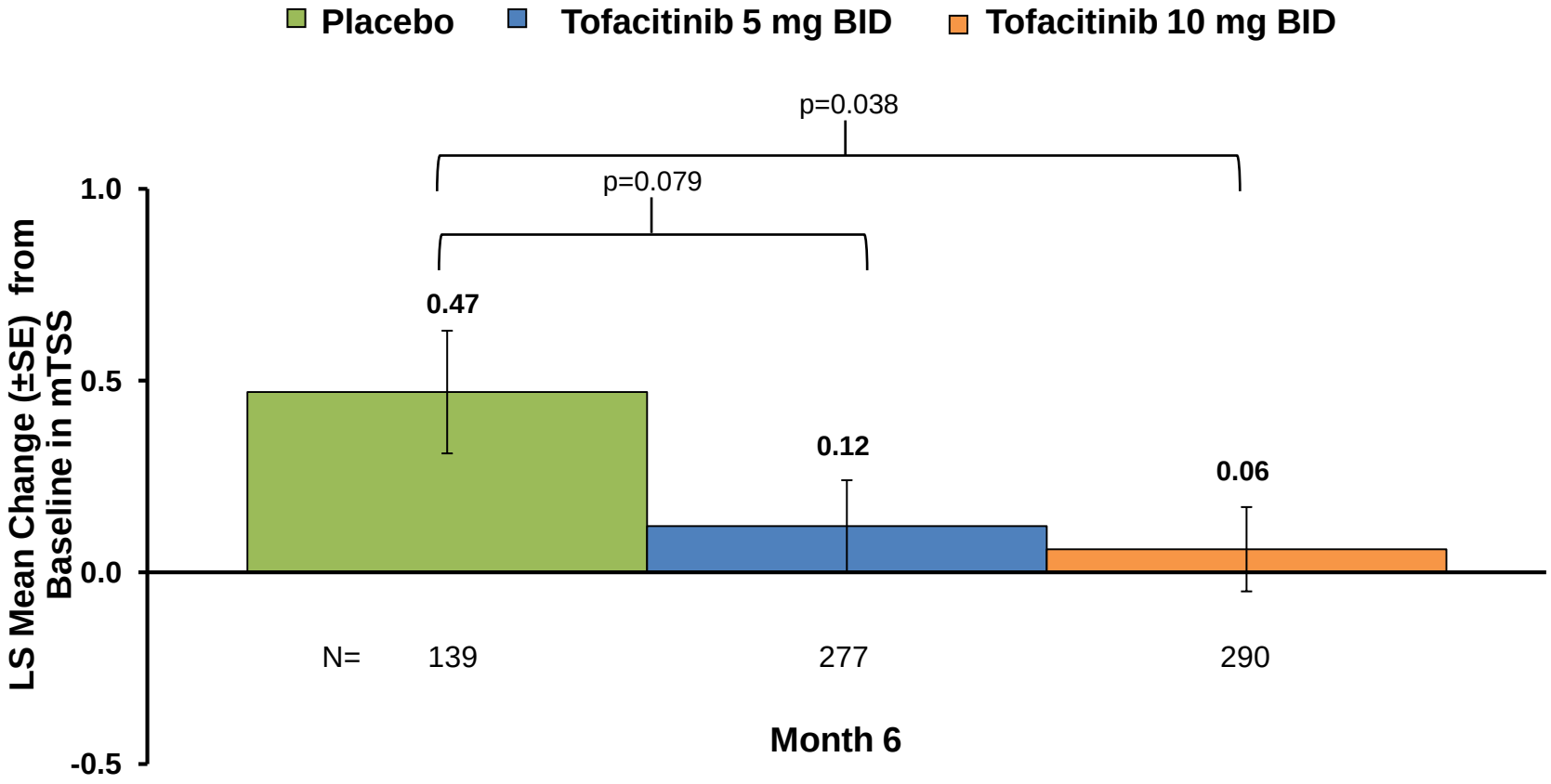
# Radiographic Methods for Scan Study

- Each patient's x-rays were scored by 2 independent trained readers blinded to treatment sequence and visit/time
  - Data averaged for each timepoint for each patient
- Linear extrapolation
  - Non-responders at Month 3 had x-rays performed
    - 49% of placebo group
    - 26% and 18% of tofacitinib 5 and 10 mg groups, respectively
  - Placebo responders had x-rays performed at Month 6
    - 51% of placebo group
  - Month 12 placebo data was all extrapolated

# Baseline Joint Damage Balanced Across Groups

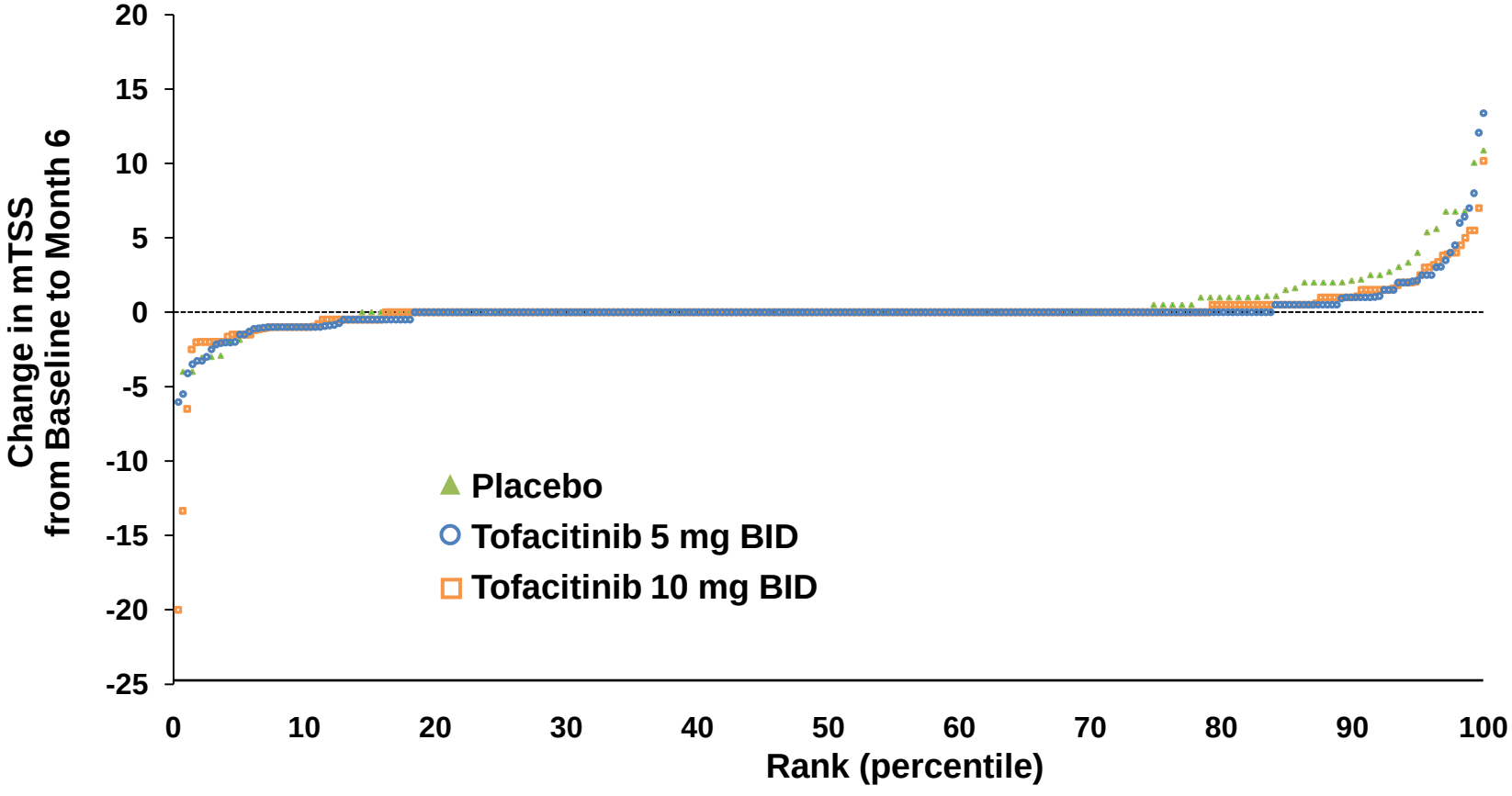
| | Tofacitinib | | | |
|---|---|---|---|---|
| | 5 mg BID N=286 | 10 mg BID N=295 | Placebo→ 5 mg BID N=71 | Placebo→ 10 mg BID N=68 |
| mTSS, mean | 31.1 | 37.3 | 35.0 | 30.1 |

# Tofacitinib Inhibited Structural Damage

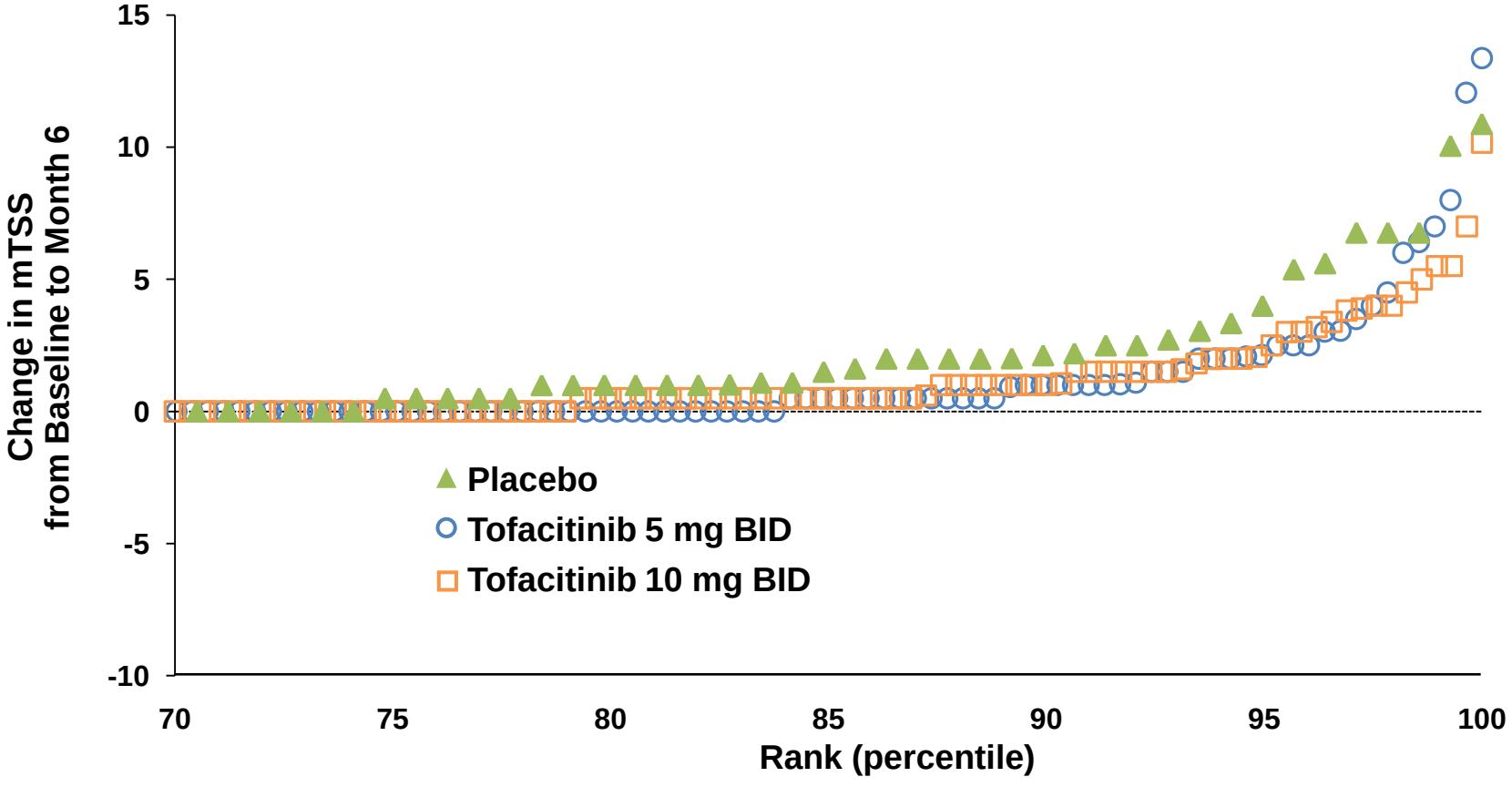



LS, least squares

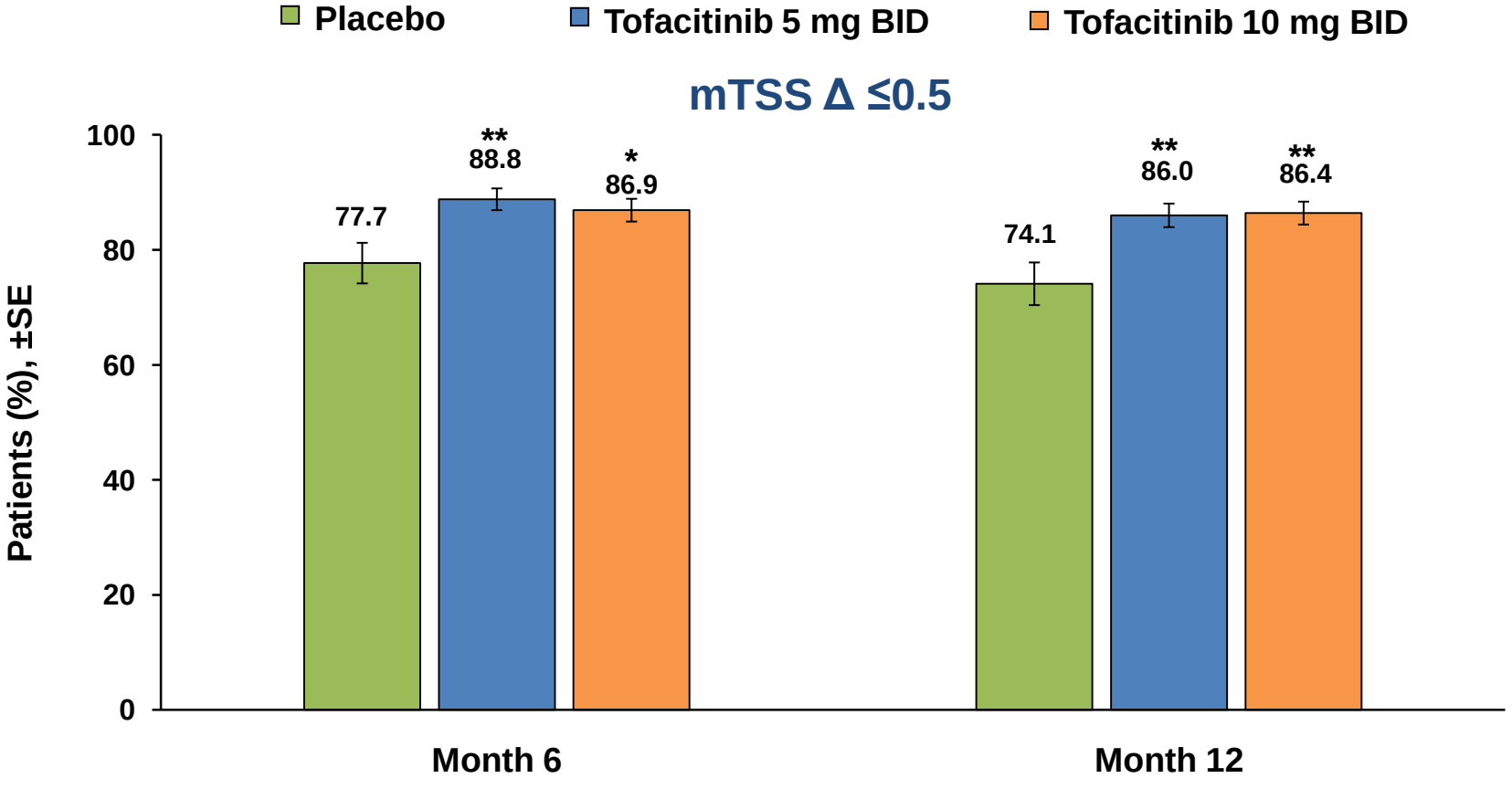
# Fewer Tofacitinib-Treated Patients had Progression of Joint Damage



# Fewer Tofacitinib-Treated Patients had Progression of Joint Damage

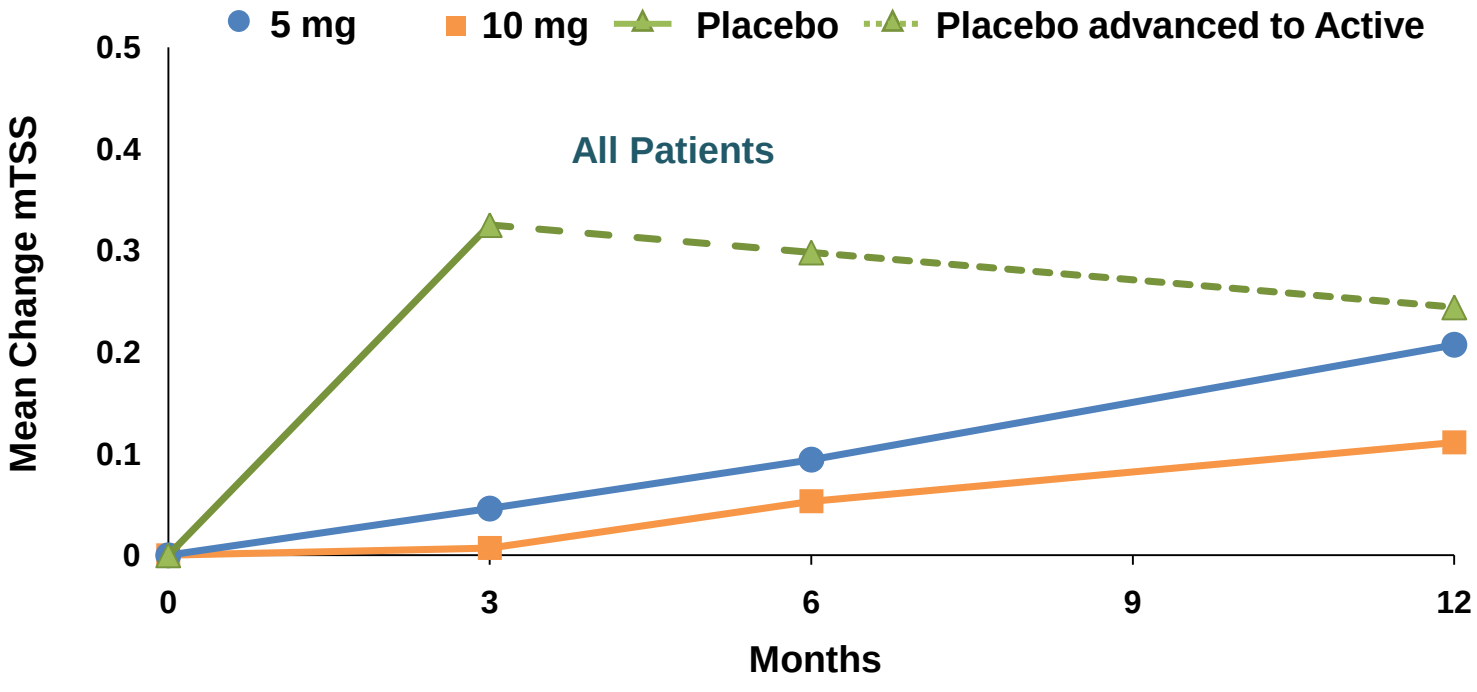


# More Tofacitinib-Treated Patients had No X-ray Progression



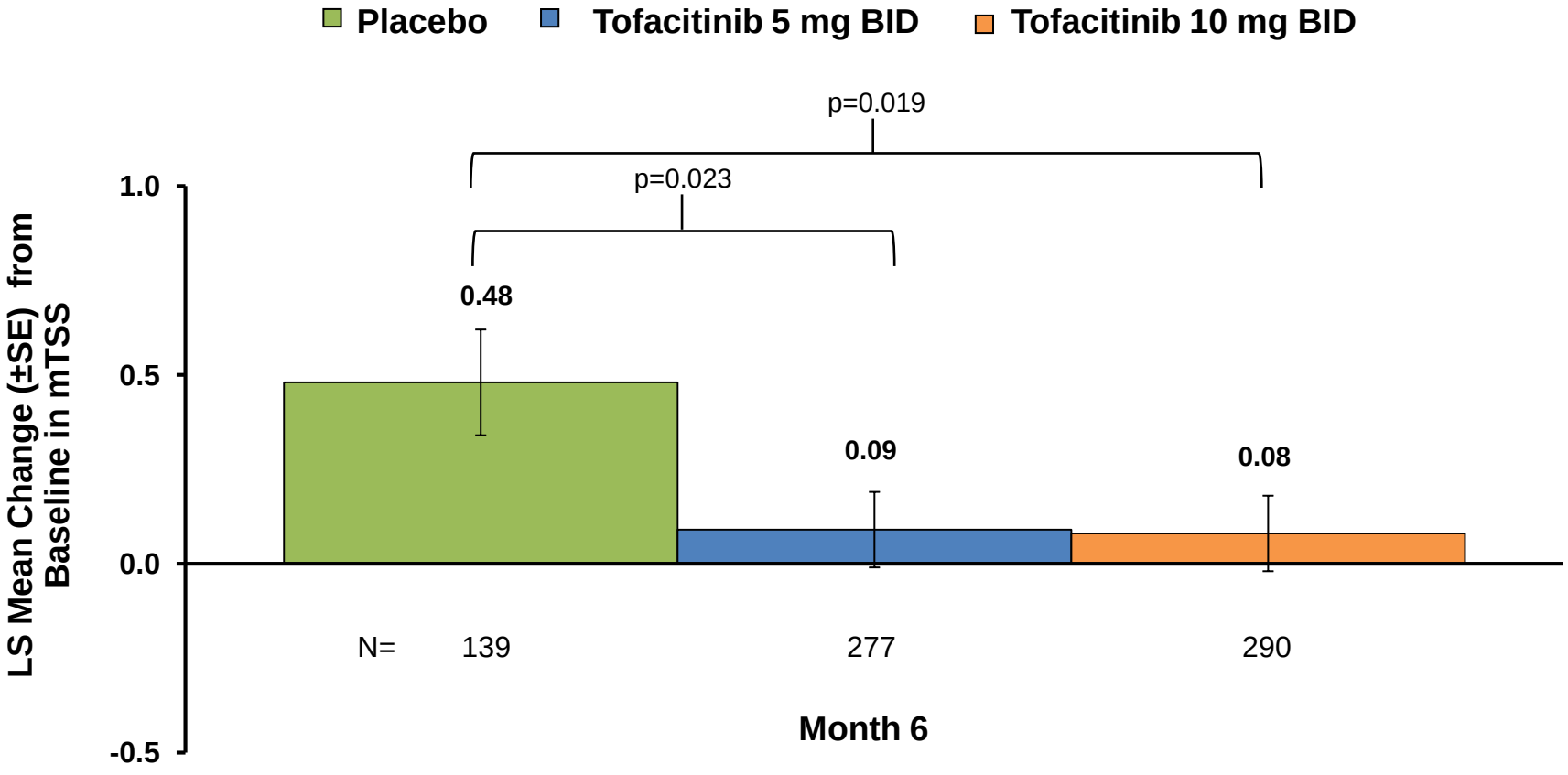

*p<0.05; **p<0.01 vs placebo

# Observed Mean Change from Baseline in mTSS by Treatment Group



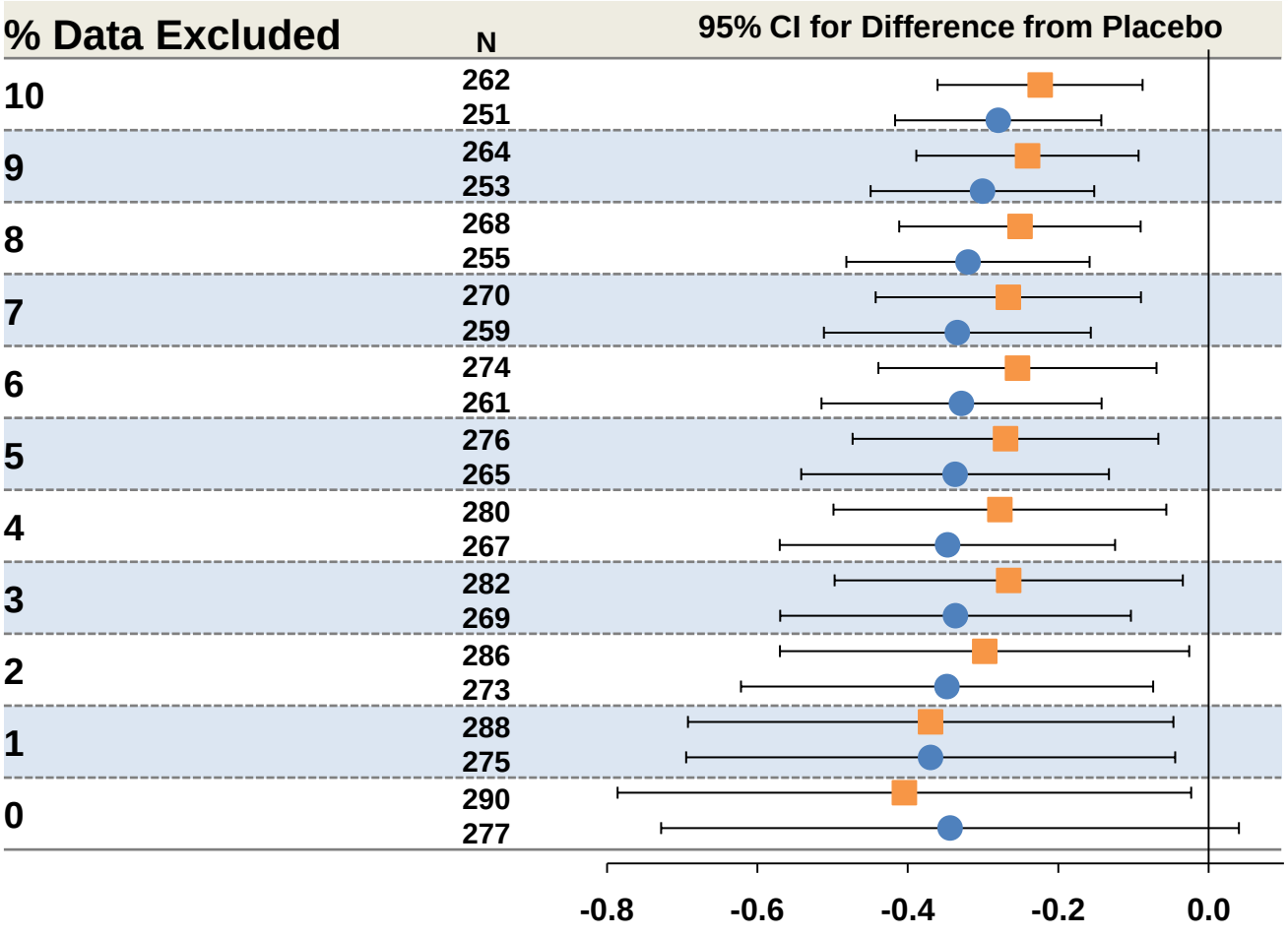

| | | | | |
|---|---|---|---|---|
| 5mg | 286 | 97 | 265 | 251 |
| 10mg | 295 | 70 | 277 | 258 |
| Placebo | 139 | 83 | 129 | 123 |

# Mean Change in mTSS at Month 6:
## "As Observed" Data Shows Inhibition of Structural Damage




LS, least squares

# Inhibition of Structural Progression Is Not Driven by "Outliers"




Tofacitinib 5 mg BID

Tofacitinib 10 mg BID

**Scan/1044 Month 12 mTSS change from baseline: data excluded 0-10%**

# Agenda

- Phase 2
- Phase 3 Study Overview
- Tofacitinib Phase 3 Efficacy Data
- Additional Efficacy Data
  - Patient-Reported Outcomes
  - Tofacitinib in subpopulations
  - Maintenance of efficacy, including long-term open-label extension studies
- Conclusion

# Broad Assessment of Patient-Reported Outcomes

- Assessed in all 5 Phase 3 studies
- Endpoints
  - HAQ-DI
  - Pain
  - Patient global assessment of arthritis
  - SF-36 (physical and mental component scores)
  - FACIT-fatigue

Functional Assessment of Chronic Illness Therapy Fatigue is abbreviated FACIT-fatigue.
Short Form 36 is abbreviated SF-36

# Significant Differences from Placebo in Patient Reported Outcomes at Month 3

| | Scan/1044 | | Sync/1046 | | Standard/1064 | | Step/1032 | | Solo/1045 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 5 mg | 10 mg | 5 mg | 10 mg | 5 mg | 10 mg | 5 mg | 10 mg | 5 mg | 10 mg |
| Patient Pain | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| Patient Global | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| HAQ-DI | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| SF-36 PCS | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |
| SF-36 MCS | √ | √ | √ | √ | NS | √ | √ | √ | √ | √ |
| FACIT-Fatigue | √ | √ | √ | √ | √ | √ | √ | √ | √ | √ |

Significant differences between tofacitinib (5 and 10 mg BID) versus placebo at Month 3 at $p < 0.05$.
(FAS, longitudinal model).

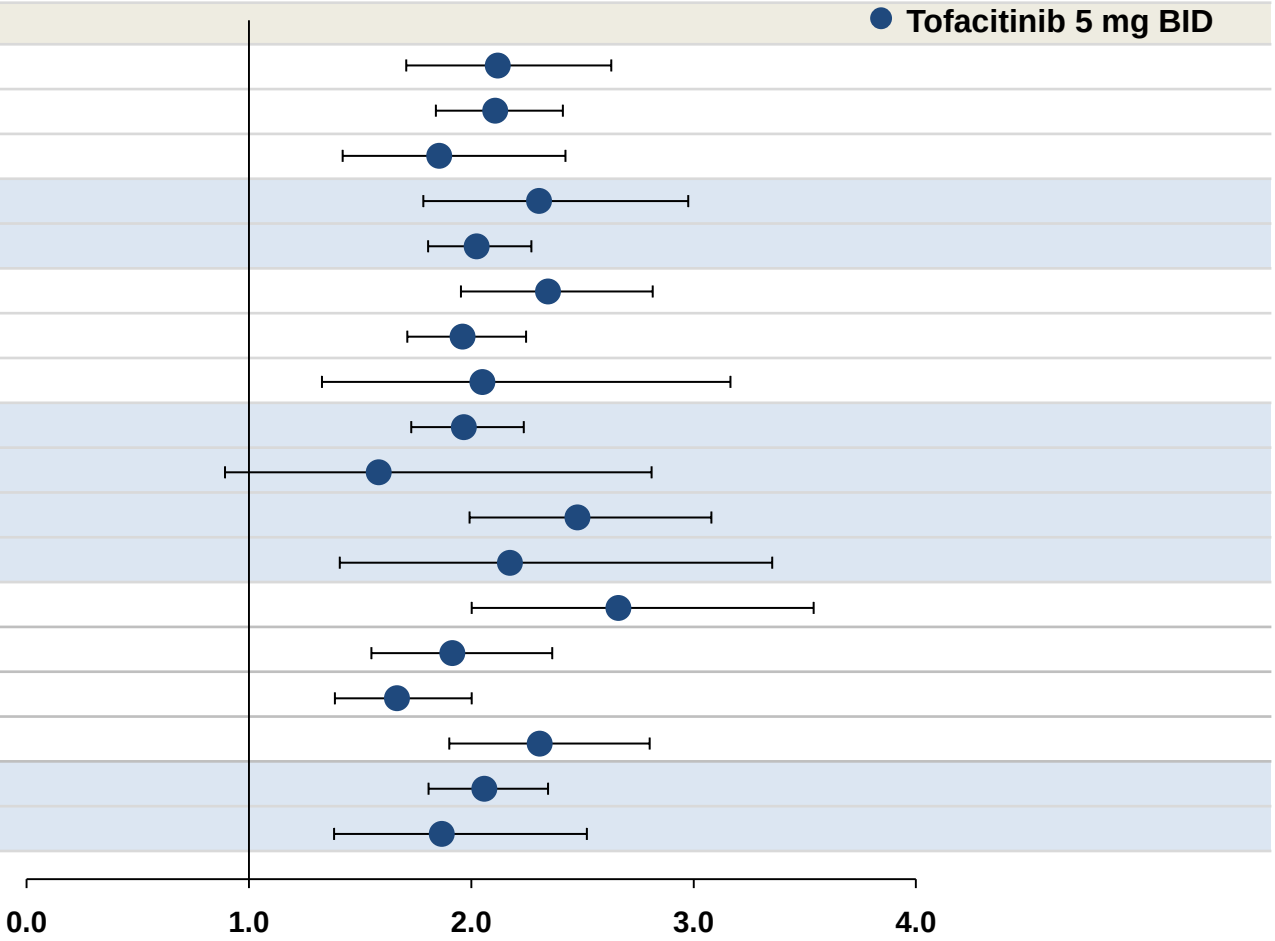
# Tofacitinib vs Adalimumab in Patient Reported Outcomes at Month 3: Standard Study

| Parameter (Range of Baseline Means) | Placebo | Tofacitinib 5 Mg | Tofacitinib 10 mg | Adalimumab |
|---|---|---|---|---|
| Patient Pain (55.20-59.29) | -9.57 | -26.85* | -28.11* | -22.26 |
| Patient Global (54.46-59.86) | -7.37 | -23.89 | -26.60* | -21.37 |
| HAQ-DI (1.42-1.53) | -0.24 | -0.55 | -0.61* | -0.49 |
| SF-36 PCS (32.62-33.10) | 3.18 | 7.08 | 7.93* | 6.19 |
| SF-36 MCS (39.82-43.29) | 1.80 | 3.33 | 6.11* | 3.40 |
| FACIT-Fatigue (27.95-30.49) | 1.56 | 5.97 | 7.00* | 4.97 |

Standard Study; *p<0.05 vs adalimumab (unadjusted)
(FAS, longitudinal model).

# Tofacitinib 5 mg BID is Efficacious Across Subgroups of Patients: Pooled Data

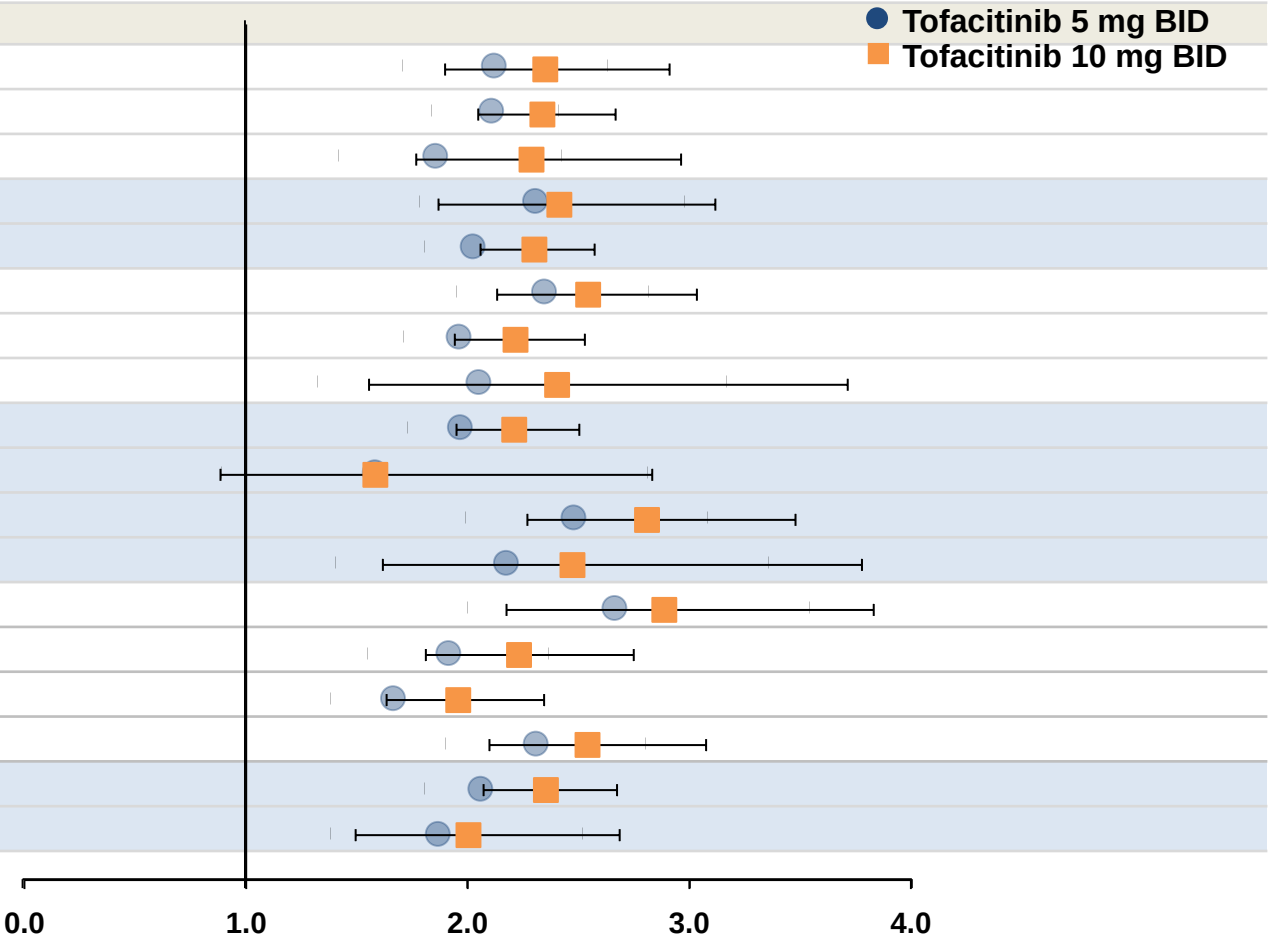
| | N |
|---|---|
| 18-44 years | 282 |
| 45-64 years | 840 |
| ≥65 years | 196 |
| Male | 211 |
| Female | 1107 |
| <60 KG | 431 |
| 60-100 KG | 785 |
| >100 | 102 |
| White | 781 |
| Black | 44 |
| Asian | 384 |
| Other | 109 |
| RA Duration: <2 | 236 |
| RA Duration: 2 to <5 | 306 |
| RA Duration: 5 to <10 | 317 |
| RA Duration: ≥10 | 459 |
| Sero: RF+ or CCP+ | 927 |
| Sero: RF- and CCP- | 196 |




ACR 20, Pooled Phase 2 and Phase 3 data

# Tofacitinib 5 mg & 10 mg BID is Efficacious Across Subgroups of Patients: Pooled Data

| | N |
|---|---|
| 18-44 years | 316 |
| 45-64 years | 804 |
| ≥65 years | 202 |
| Male | 206 |
| Female | 1116 |
| <60 KG | 433 |
| 60-100 KG | 791 |
| >100 | 98 |
| White | 790 |
| Black | 36 |
| Asian | 365 |
| Other | 131 |
| RA Duration: <2 | 224 |
| RA Duration: 2 to <5 | 312 |
| RA Duration: 5 to <10 | 332 |
| RA Duration: ≥10 | 454 |
| Sero: RF+ or CCP+ | 897 |
| Sero: RF- and CCP- | 226 |

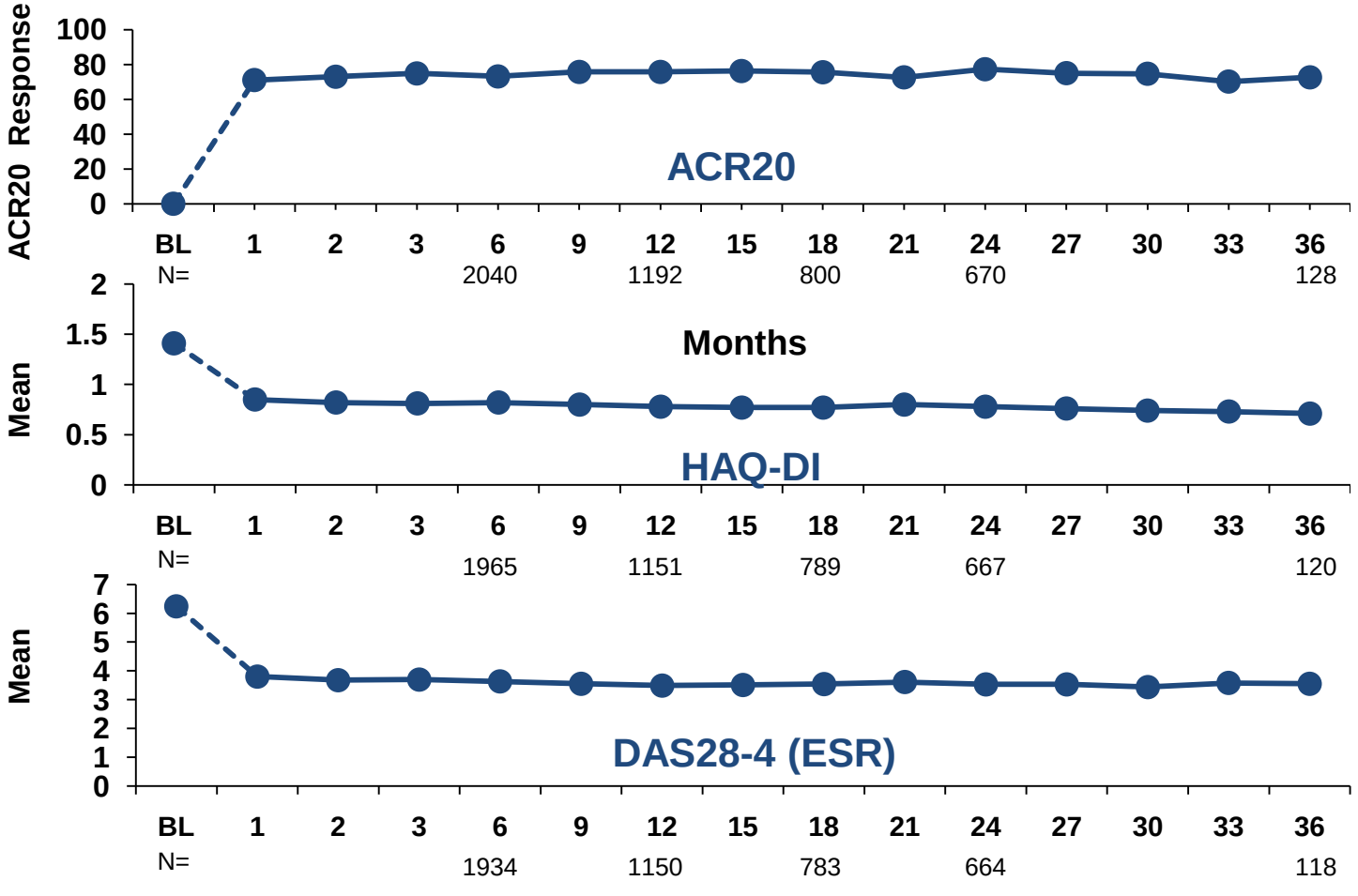



ACR20, Pooled Phase 2 and Phase 3 data

# Broad Participation in Long-Term Extension Studies

- Over 3000 patients from the Phase 2/Phase 3 program have entered ongoing, open-label, long-term follow-up studies
- Overall retention rate approximately 82%
- ACR responses, HAQ-DI, and DAS28 efficacy data available for up to 3 years
- Two-year efficacy data available in over 650 patients with 3-year data available in over 100 patients

# Tofacitinib Efficacy is Maintained for 3 years




Change from pretreatment baseline

# Agenda

- Phase 2
- Phase 3 Study Overview
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- Additional Efficacy Data
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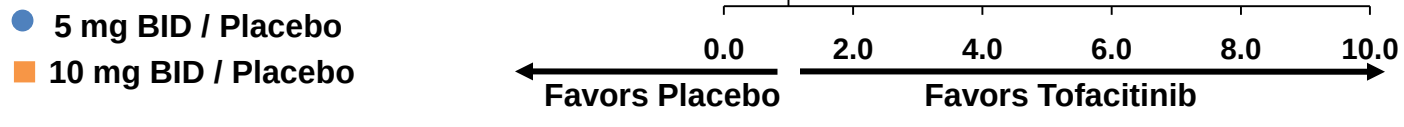
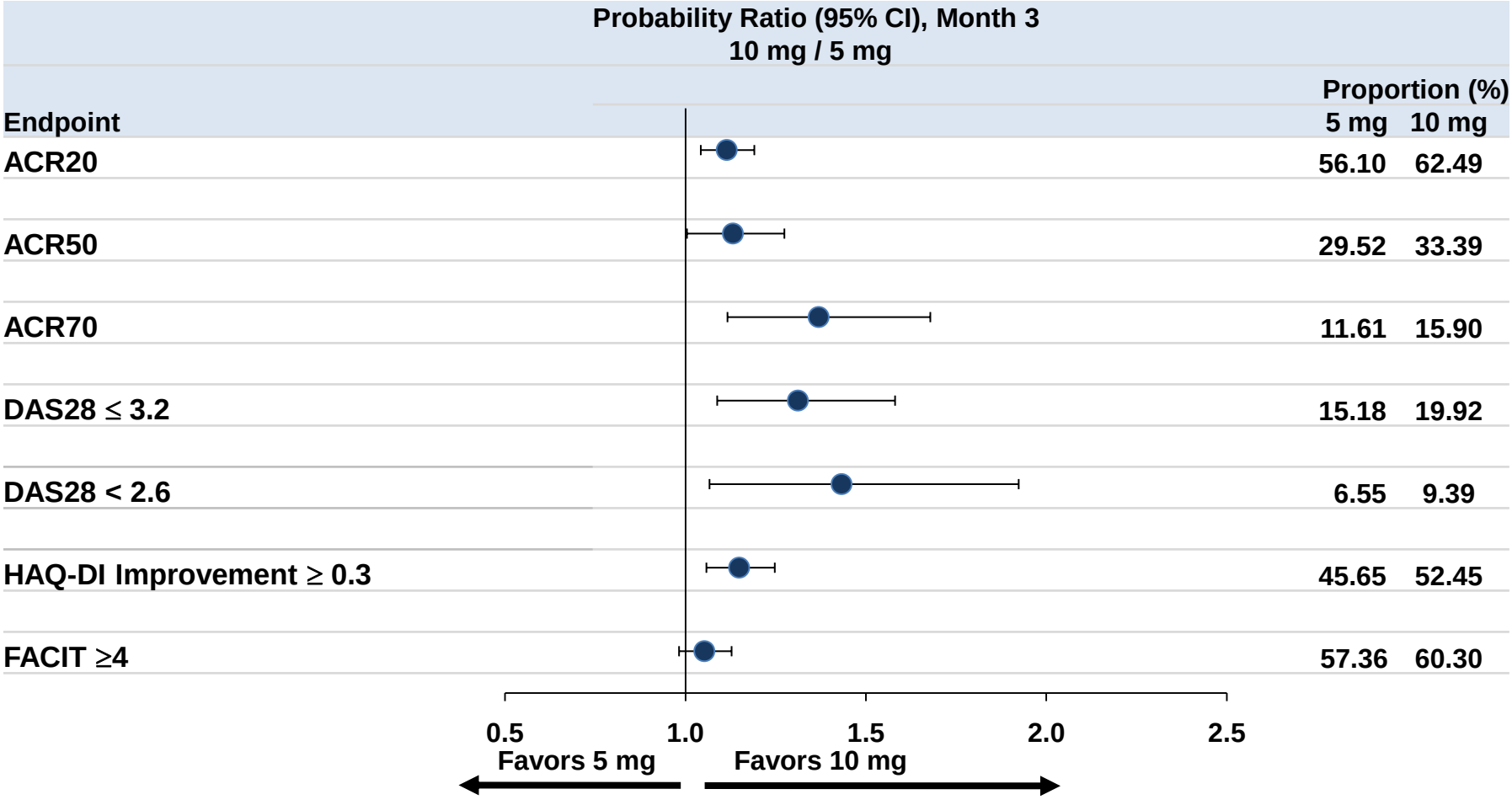
  - Tofacitinib in subpopulations
  - Maintenance of efficacy, including long-term open-label extension studies
- Conclusion

# Clinically Meaningful Efficacy at Both 5 and 10 mg BID

| Endpoint | Comparison | Month 3 Probability Ratio (95% CI) | Proportion (%) Drug | Placebo |
|---|---|---|---|---|
| ACR20 | 5 mg vs Pbo | | 56.10 | 26.50 |
| | 10 mg vs Pbo | | 62.49 | |
| ACR50 | 5 mg vs Pbo | | 29.52 | 8.98 |
| | 10 mg vs Pbo | | 33.39 | |
| ACR70 | 5 mg vs Pbo | | 11.61 | 2.69 |
| | 10 mg vs Pbo | | 15.90 | |
| DAS28 ≤ 3.2 | 5 mg vs Pbo | | 15.18 | 4.16 |
| | 10 mg vs Pbo | | 19.92 | |
| DAS28 < 2.6 | 5 mg vs Pbo | | 6.55 | 1.83 |
| | 10 mg vs Pbo | | 9.39 | |
| HAQ-DI ≥ 0.3 | 5 mg vs Pbo | | 45.65 | 23.42 |
| | 10 mg vs Pbo | | 52.45 | |
| FACIT ≥ 4 | 5 mg vs Pbo | | 57.36 | 38.66 |
| | 10 mg vs Pbo | | 60.30 | |



# Improved Clinical Efficacy of 10 mg Compared to 5 mg



# Tofacitinib 5 and 10 mg BID are Effective

- In patients with moderately to severely active RA
  - As monotherapy and  in combination with nonbiologic DMARDs
- In patients across a range of previous treatment experience
  - DMARD inadequate responders
  - TNF inhibitor inadequate responders
- Consistent effects on:
  - Signs and symptoms
  - Progression of structural damage
  - Patient reported outcomes, eg physical functioning and HRQOL
- Onset of response within 2 weeks; Efficacy maintained for up to 3 years

# Tofacitinib: Safety Review

**Richard Riese, M.D., Ph.D.**

**Senior Director, Tofacitinib RA Program**

**Pfizer, Inc.**

# Safety Review Agenda

- Safety Database Overview
- General Safety
- Safety Topics of Special Interest
- Laboratory Changes
- Conclusions

# Global Safety Database

- Large, ongoing global program
  - 572 principal investigators in 44 countries
    - Tofacitinib: Approximately 4800 patients for 7000 patient-years

| Duration | Number of Patients |
|---|---|
| **≥ 6 months** | **4053** |
| **≥ 1 year** | **3384** |
| **≥ 2 years** | **989** |
| **> 3 years** | **567** |

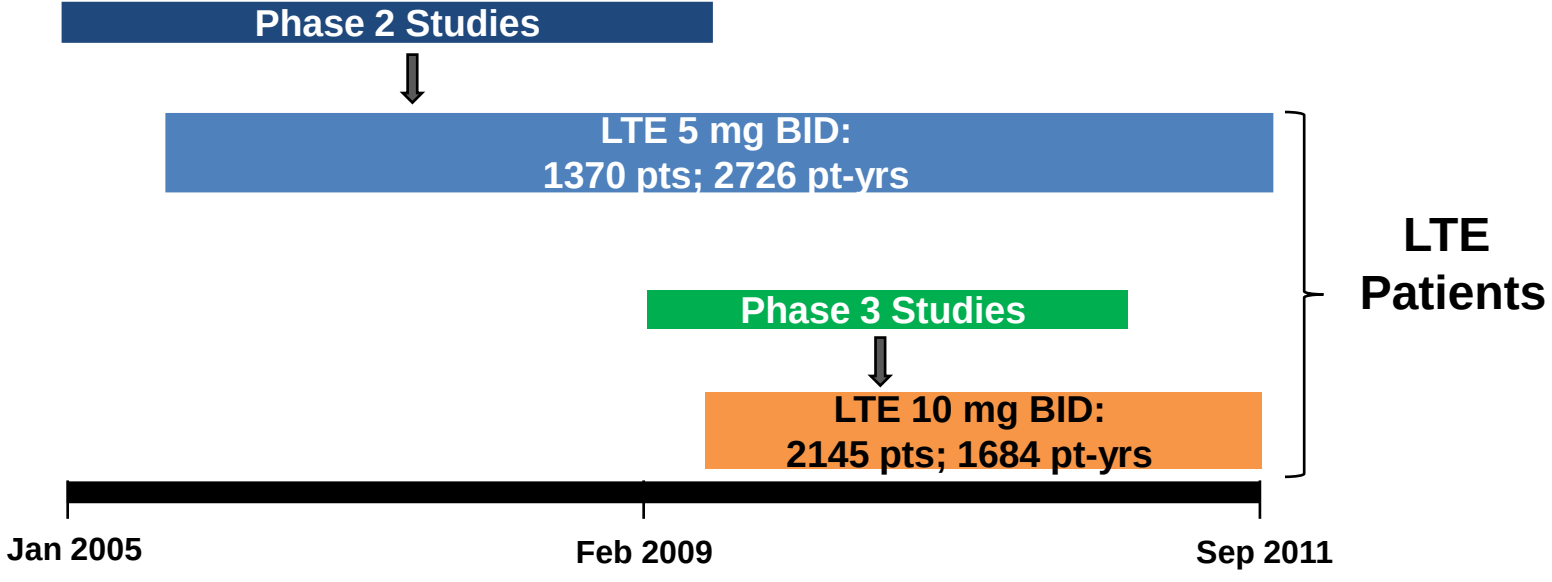
- Limited patients and patient-yrs for placebo (681 pts, 202 pt-yrs) and adalimumab (204 pts, 179 pt-yrs) in Phase 3

# Global Safety Database

- Diverse demographics, geographies and co-morbidities
  - Approximately 15% aged ≥65 years (505 in Phase 3)
  - Representative co-morbidities
    - Diabetes
    - Hypertension
    - Cardiovascular disease
    - High cholesterol

# Long Term Extension Studies
## Differences Between the 5 and 10 mg Dose Groups

- Inclusion of large, open-label long-term extension (LTE) studies allows for safety assessments over the longer-term
  - Dose differences in the LTEs should be interpreted with caution



# Safety Review Agenda

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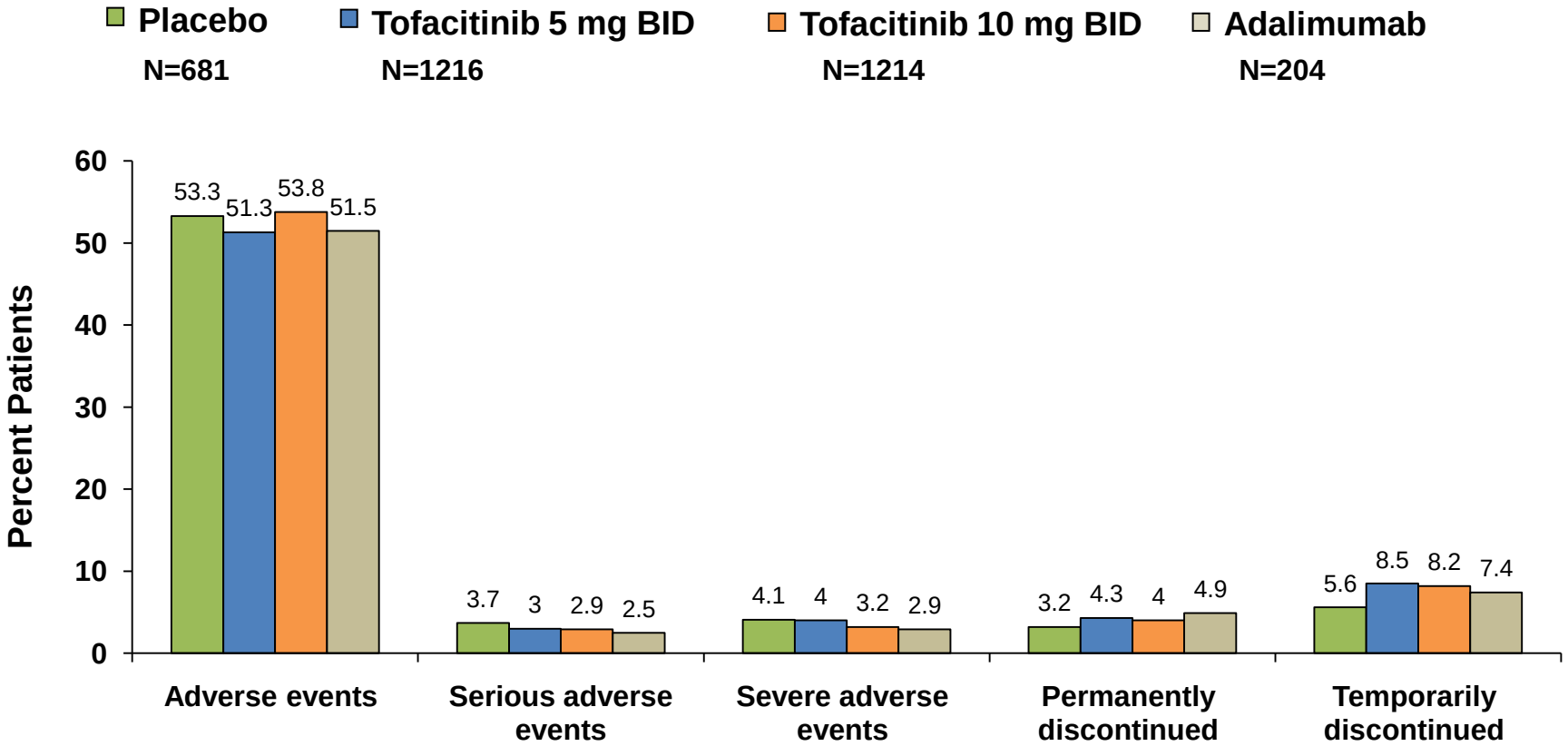
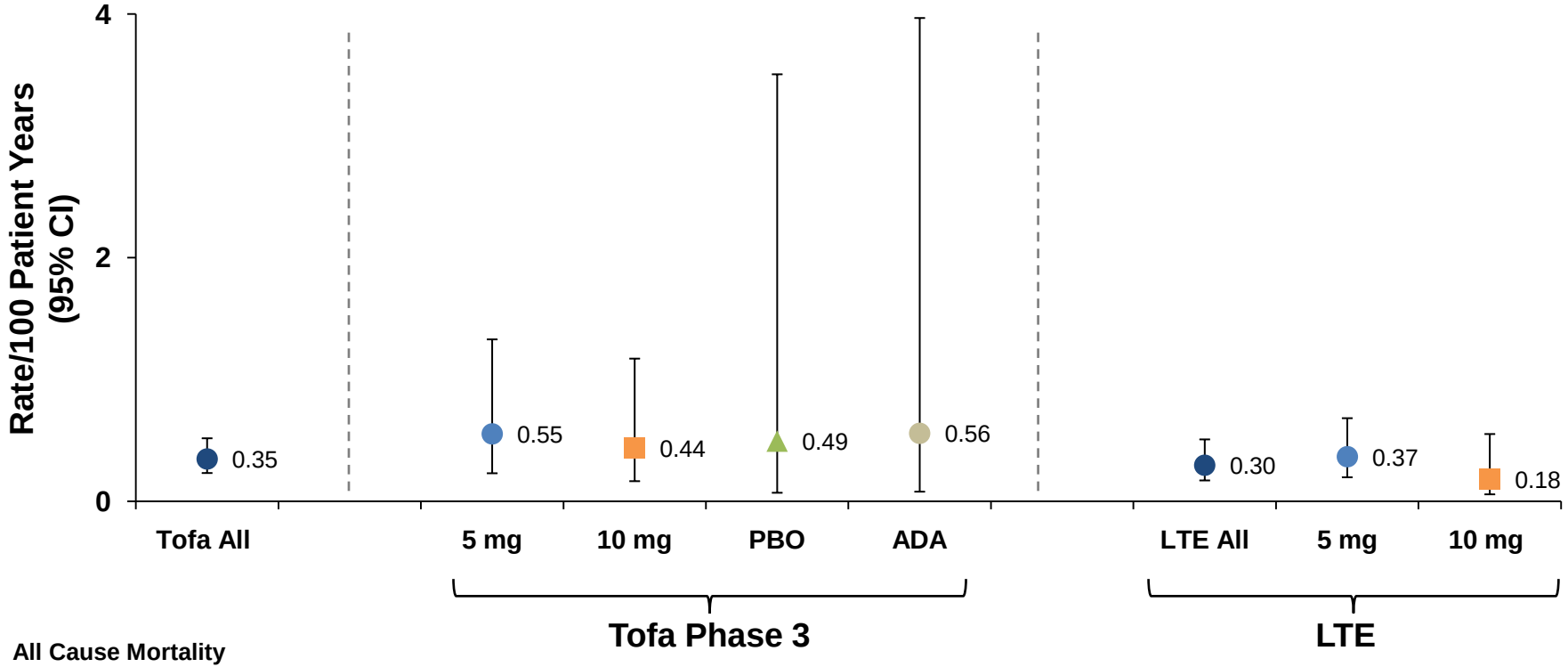
# General Safety Assessments
# Controlled Phase 3 Studies (0 to 3 Months)




Data as of 29Mar2011

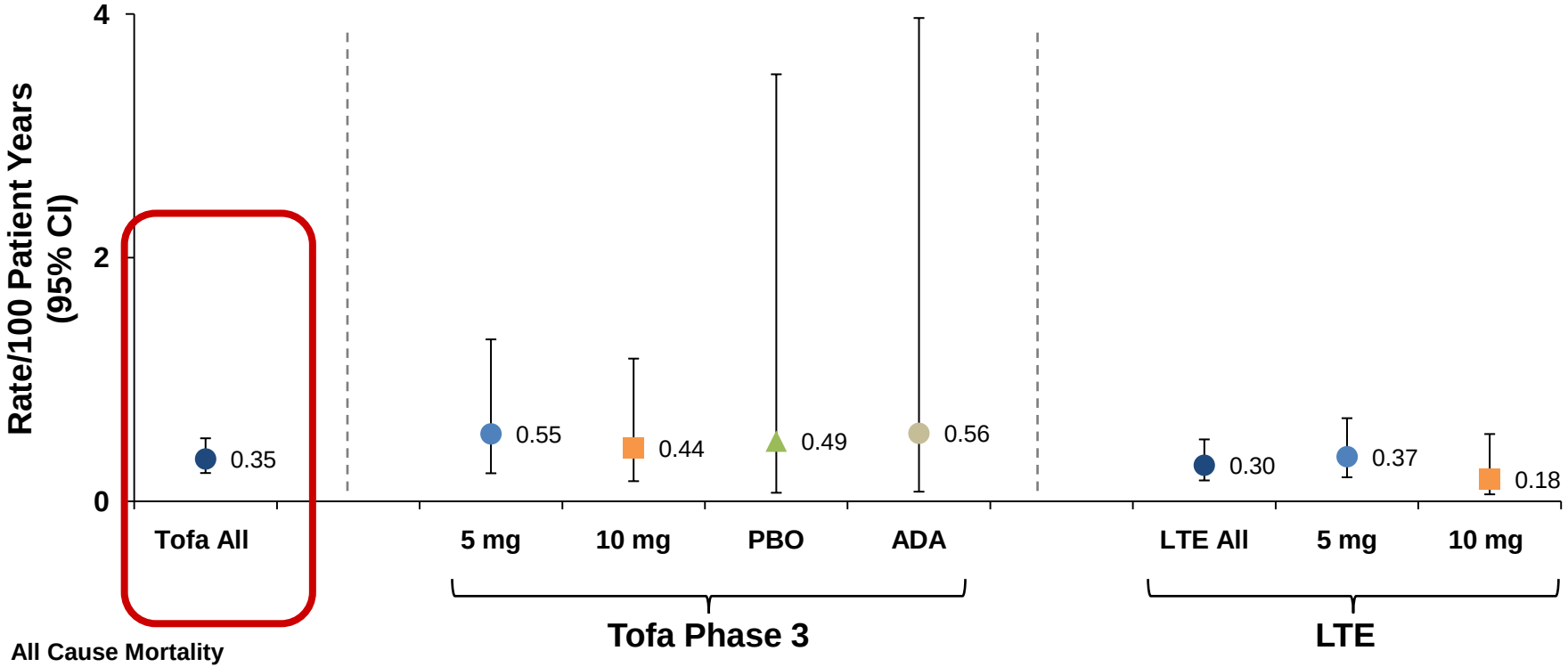
# Mortality Rates Consistent Across Dose Groups




**All Cause Mortality**
Bars for CP indicate 95% Confidence Limits
Incidence rate of patients per 100 pt-yrs
*Deaths occurring within 30 days of discontinuing drug are included in the graph

**Data as of 29SEP2011**

# Mortality Rates
# Consistent Across Dose Groups

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Bars for CP indicate 95% Confidence Limits
Incidence rate of patients per 100 pt-yrs
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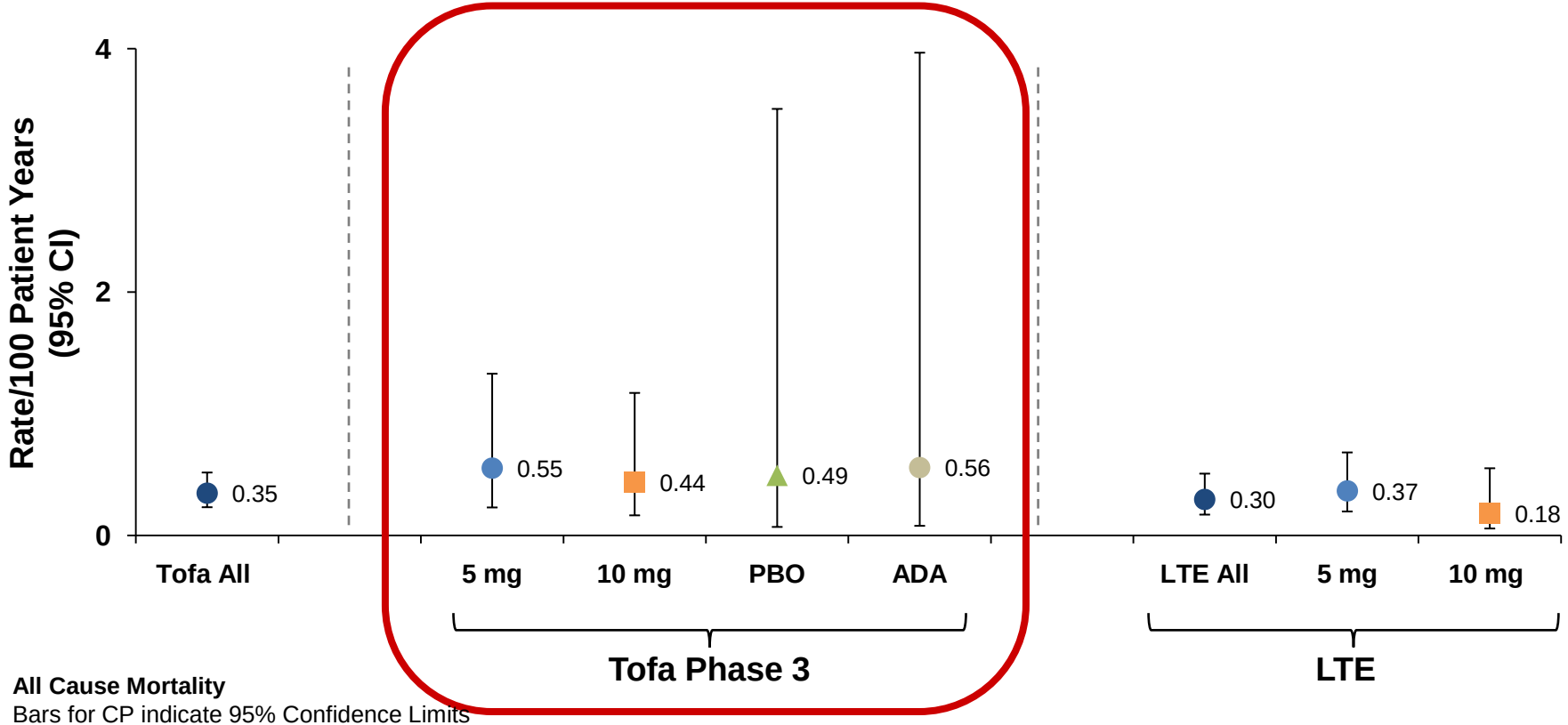
**Data as of 29SEP2011**

# Mortality Rates
# Consistent Across Dose Groups




**All Cause Mortality**
Bars for CP indicate 95% Confidence Limits
Incidence rate of patients per 100 pt-yrs
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**Data as of 29SEP2011**

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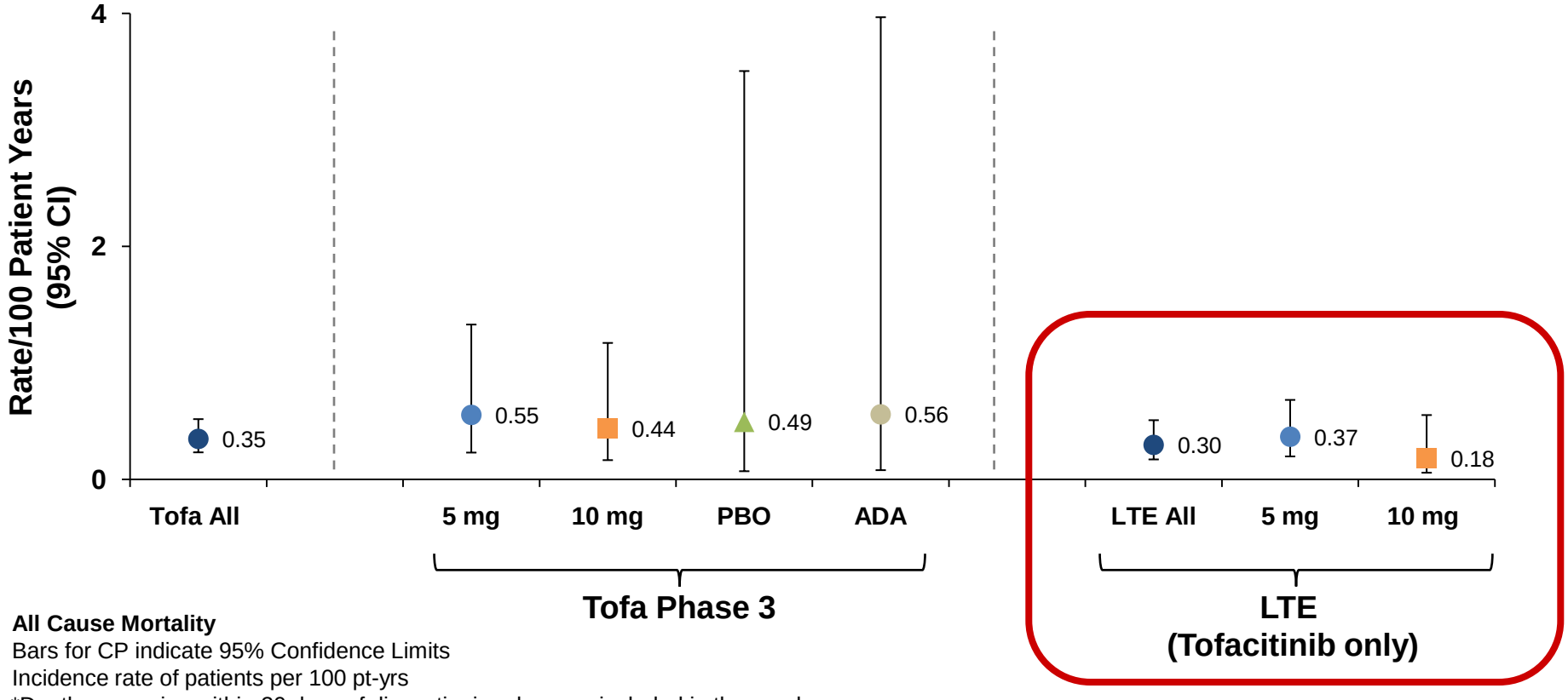
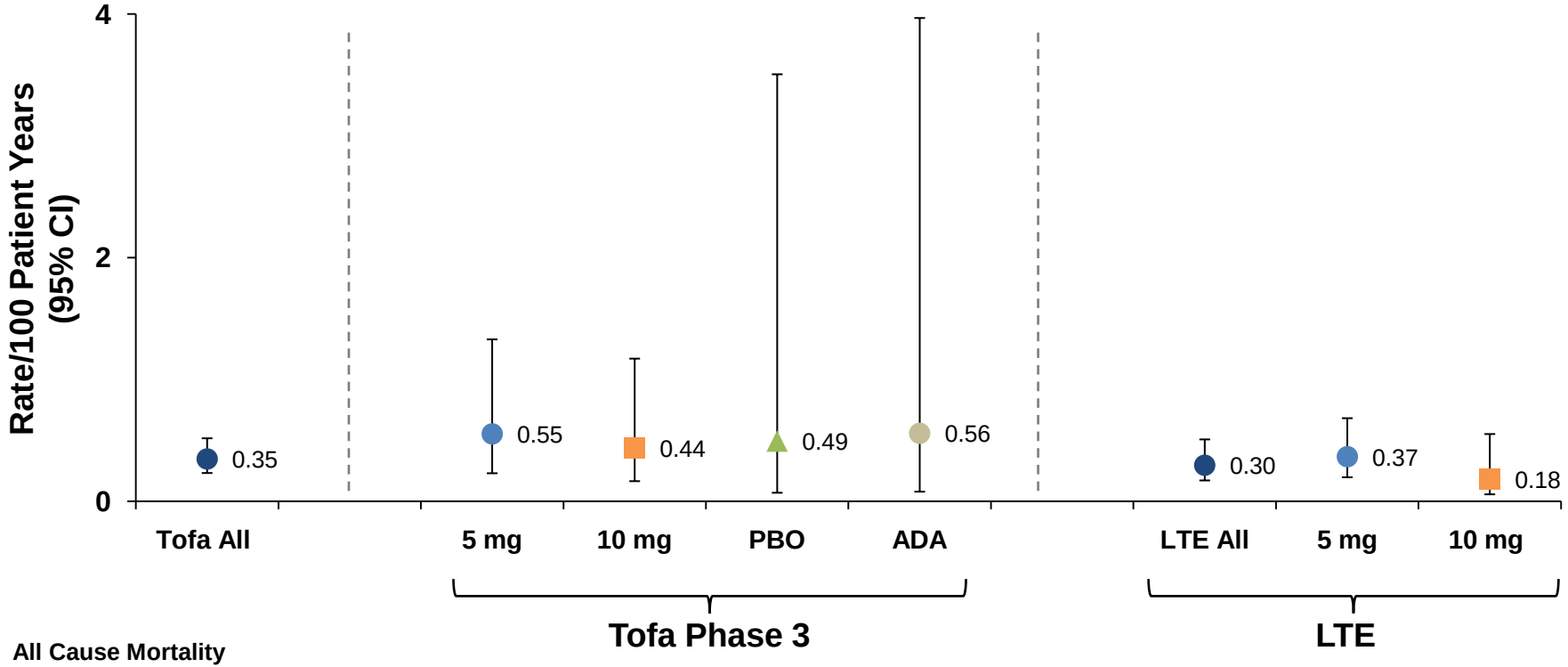
# Consistent Across Dose Groups




**All Cause Mortality**
Bars for CP indicate 95% Confidence Limits
Incidence rate of patients per 100 pt-yrs
*Deaths occurring within 30 days of discontinuing drug are included in the graph

**Data as of 29SEP2011**

# Mortality Rates
# Consistent Across Dose Groups




**All Cause Mortality**
Bars for CP indicate 95% Confidence Limits
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*Deaths occurring within 30 days of discontinuing drug are included in the graph

**Data as of 29SEP2011**

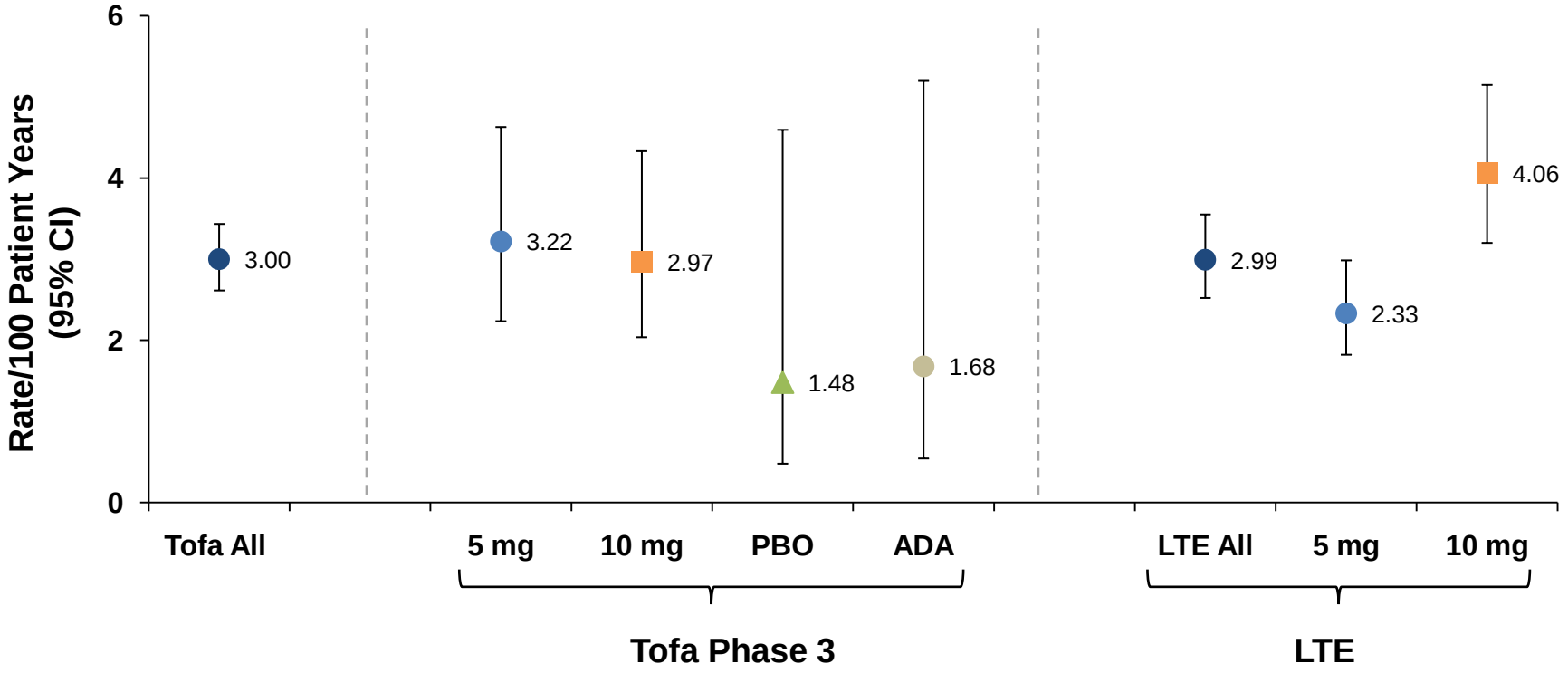
# Safety Topics of Special Interest

- Serious and other Important Infections
- Malignancies
- Lipids and Cardiovascular Safety
- Hepatic Safety
- GI Perforations

# Safety Topics of Special Interest

- Serious and other Important Infections
  - Tuberculosis and opportunistic infections
  - Herpes zoster
- Malignancies
- Lipids and Cardiovascular Safety
- Hepatic Safety
- GI Perforations

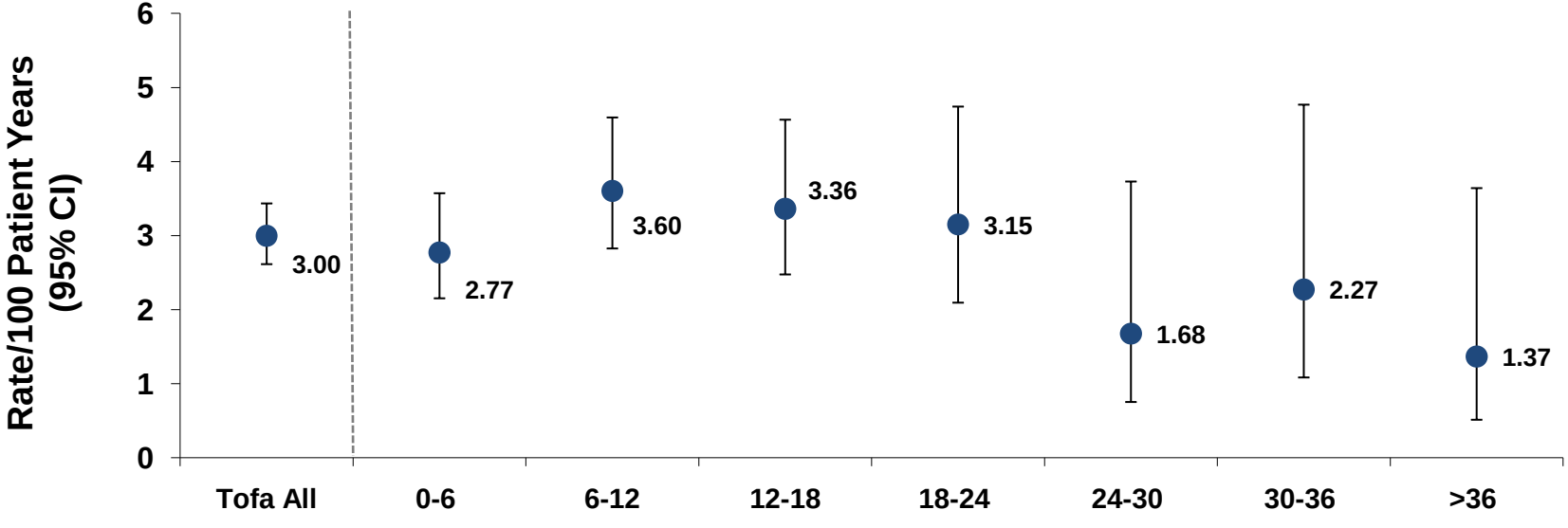
# Serious Infections: Incidence Rate 3 per 100 Patient-years




Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs

**Data as of 29SEP2011**

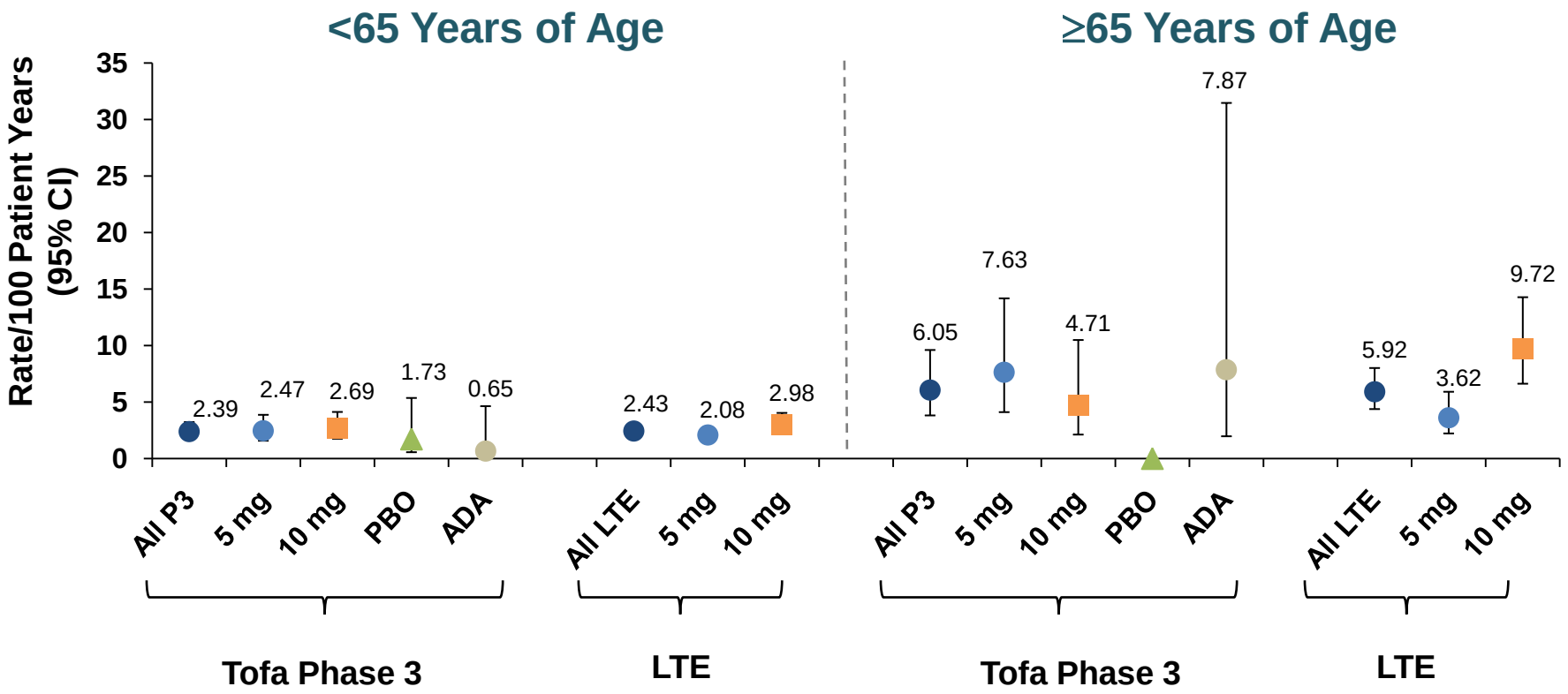
# Serious Infections Rates Stable Over Time




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Pts with events** | **206** | **60** | **65** | **41** | **23** | **6** | **7** | **4** |
| **Number of Pts** | **4791** | **4791** | **4003** | **3106** | **2037** | **930** | **663** | **555** |

Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
**Data as of 29SEP2011**

# Serious Infections by Age




Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs

**Data as of 29SEP2011**

# Tuberculosis (TB)
# Higher Incidence in Endemic Countries

- 12 patients experienced active TB on tofacitinib
  - 3 patients on 5 mg and 9 patients on 10 mg BID
  - In 8 patients TB was confined to the lung and 4 included extra-pulmonary involvement
- One (1) patient with TB in the US
  - Patient diagnosed 2 months after discontinuation of tofacitinib
- Remaining patients were in countries with higher rates of TB including China, India, Korea, Mexico, Philippines and Thailand

Data as of 29SEP2011

# Opportunistic Infections

| Infection/Organism | Number of Patients | |
|---|---|---|
| | 5 mg | 10 mg |
| Esophageal Candidiasis | 4 | 3 |
| CMV | 2 | 2 |
| Pneumocystis jiroveci | 2 | 1 |
| Cryptococcus | 1 | 2 |
| Atypical mycobacterium | 1 | 1 |
| Herpes zoster (multi-dermatomal) | 1 | 0 |
| BK encephalitis | 1 | 0 |

Data as of 29SEP2011

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Data as of 29SEP2011

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Data as of 29SEP2011

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Data as of 29SEP2011

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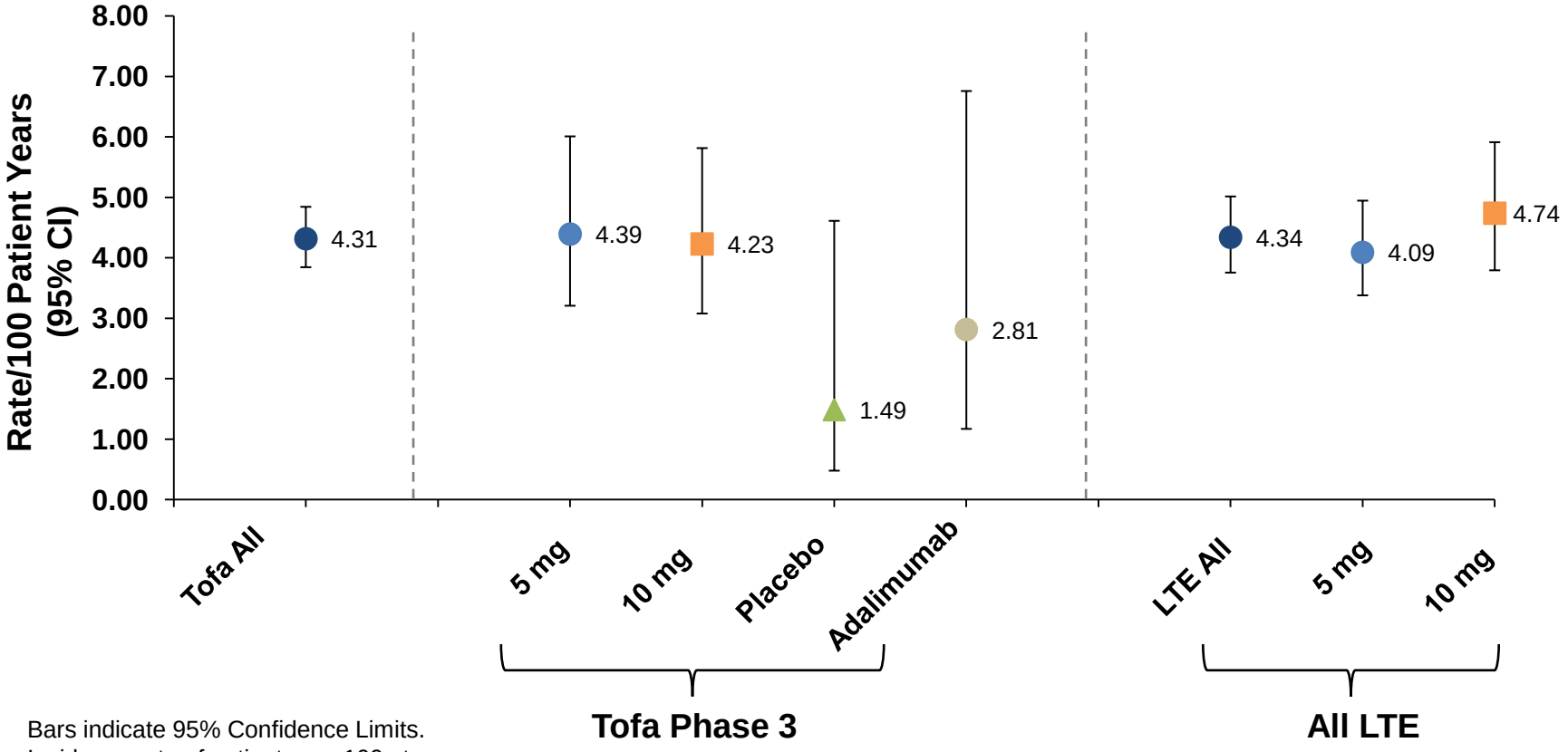
Data as of 29SEP2011

# All Herpes Zoster (Non-serious and Serious) Rates Across Dose Groups




Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs

**Data as of 29SEP2011**

# Herpes Zoster: Complications and Serious

- Complications
  - Multi-dermatomal: One patient; no patients with visceral dissemination
  - Post-herpetic Neuralgia: 4.9% of patients with zoster
  - Herpes zoster Ophthalmicus: Two (2) patients
- Serious Herpes Zoster
  - 19 patients: no patients in the US
  - Criteria for Seriousness included hospitalization and IV antivirals
  - All patients responded to appropriate medical management

# Action Plan for Herpes Zoster

- Recommendation that patients are appropriately immunized prior to tofacitinib therapy*
- For ongoing and future clinical trials:
  - Planned Adjudication of Opportunistic Infections to include:
    - Serious and multi-dermatomal/disseminated zoster
    - Post-herpetic neuralgia
    - Zoster ophthalmicus
  - Targeted data collection including history of herpes zoster and vaccination history

*Advisory Committee on Immunization Practices

# Risk Assessment: Infection

| Clinical/Observational Studies | Assessment |
|---|---|
| Ongoing and long-term extension clinical studies | • Incidence rates<br>• Type/nature<br>• Severity/seriousness<br>• Adjudication of opportunistic infections |
| Specialty clinical studies (ongoing) | • Efficacy and safety of pneumococcal and influenza vaccines in tofacitinib-treated RA patients<br>• Effects of tofacitinib on lymphocyte sub-populations |
| CORRONA and European registries | • Incidence rates of serious and other important infections (including opportunistic)<br>• Comparison to other DMARDs among all users of tofacitinib |

# Risk Mitigation: Infection

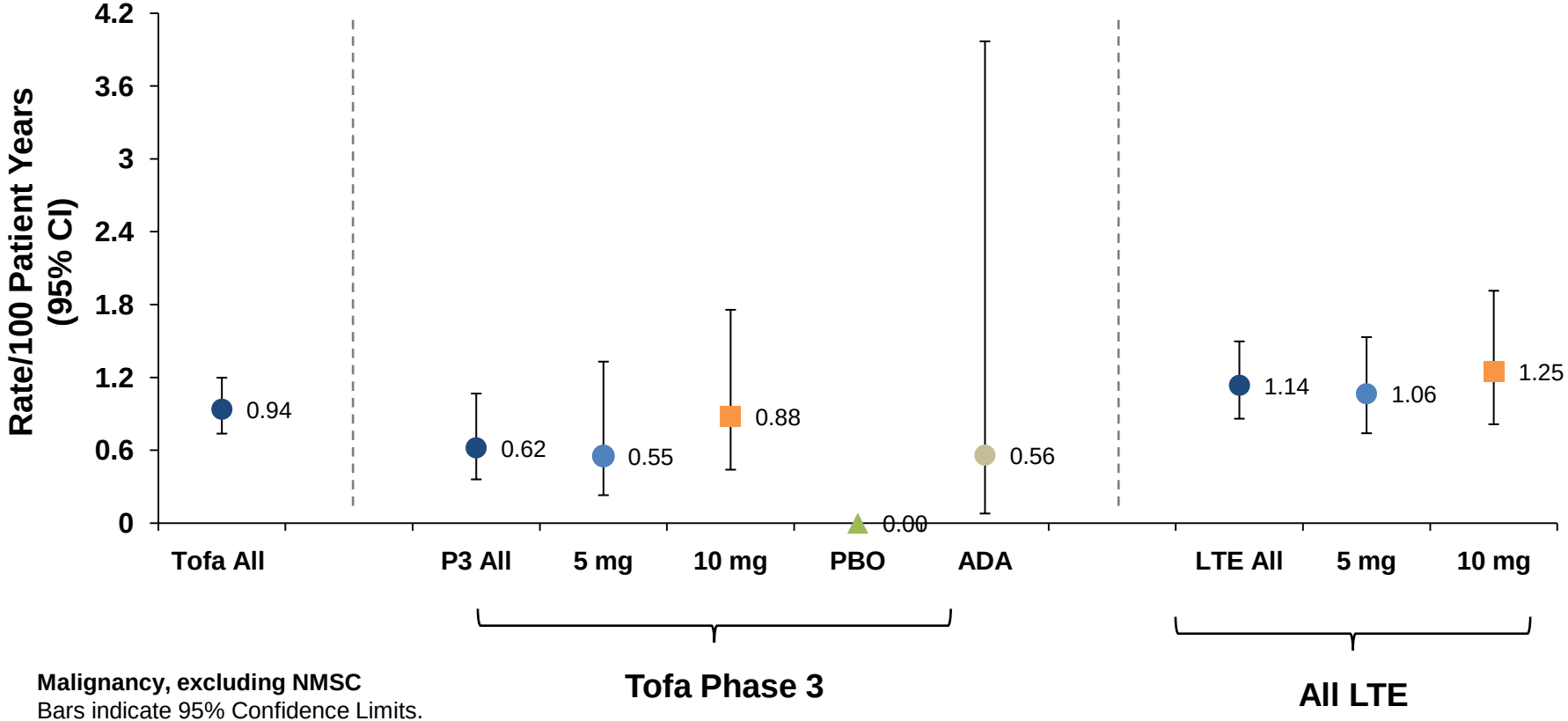
| Boxed warnings | Serious infections |
|---|---|
| Warnings and Precautions | • Tofacitinib should not be initiated in patients with an active infection<br>• Tofacitinib should be interrupted if a patient develops a serious infection, opportunistic infection or sepsis<br>• Patients should undergo TB screening prior to tofacitinib therapy<br>• If positive, initiate latent TB treatment prior to tofacitinib therapy<br>• Live attenuated vaccines should not be given while on tofacitinib |

- **Exercise caution for 10 mg BID in patients for ≥65 yrs of age; a population at increased risk for serious infection**

# Safety Topics of Special Interest

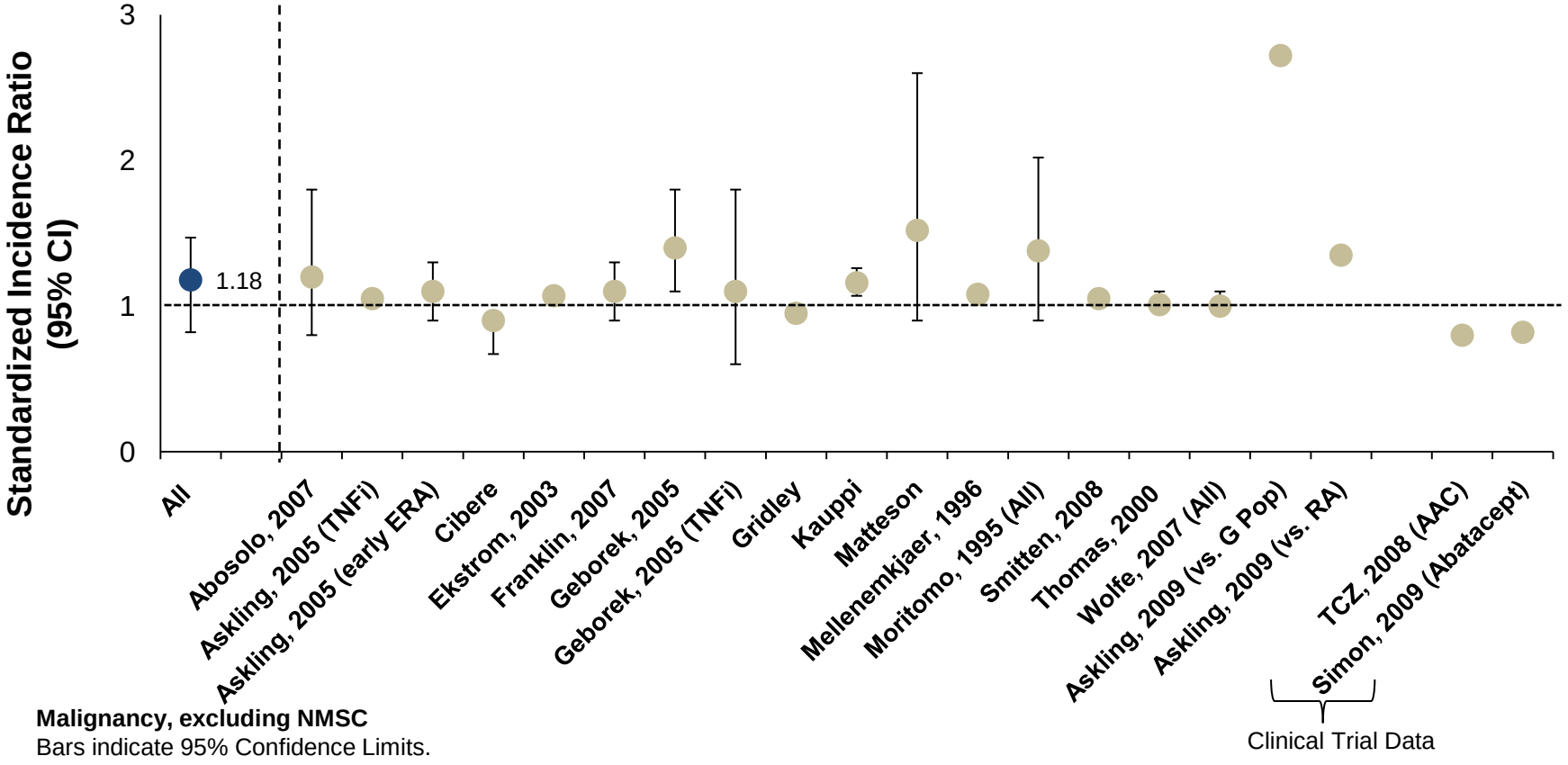
- Serious and other Important Infections
- Malignancies
  - Lymphomas
  - Lung cancer
  - Non-melanoma skin cancer
- Lipids and Cardiovascular Safety
- Hepatic Safety
- GI Perforations

# Malignancy (excluding NMSC) Rates Across Dose Groups



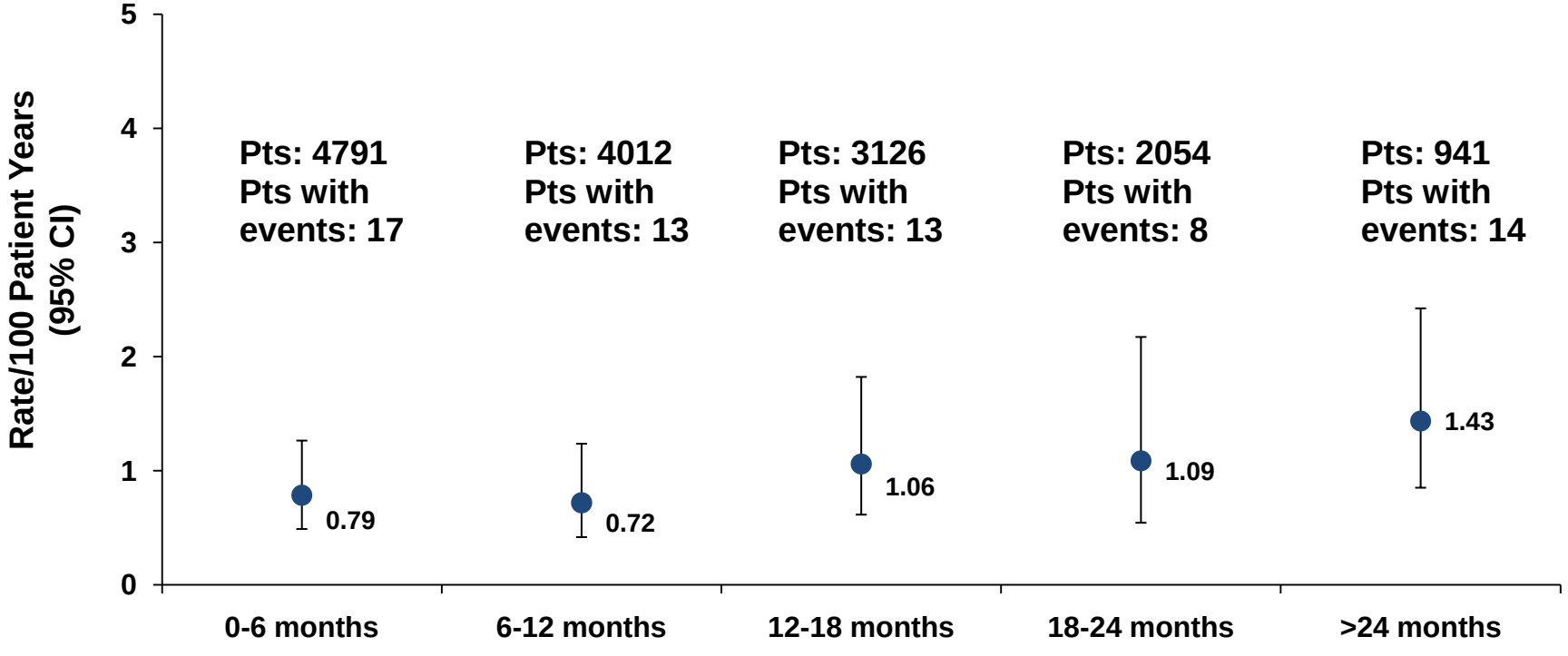

**Malignancy, excluding NMSC**
Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
**Data as of 29SEP2011**

# Malignancy: Standardized Incidence Ratio Consistent with US Population



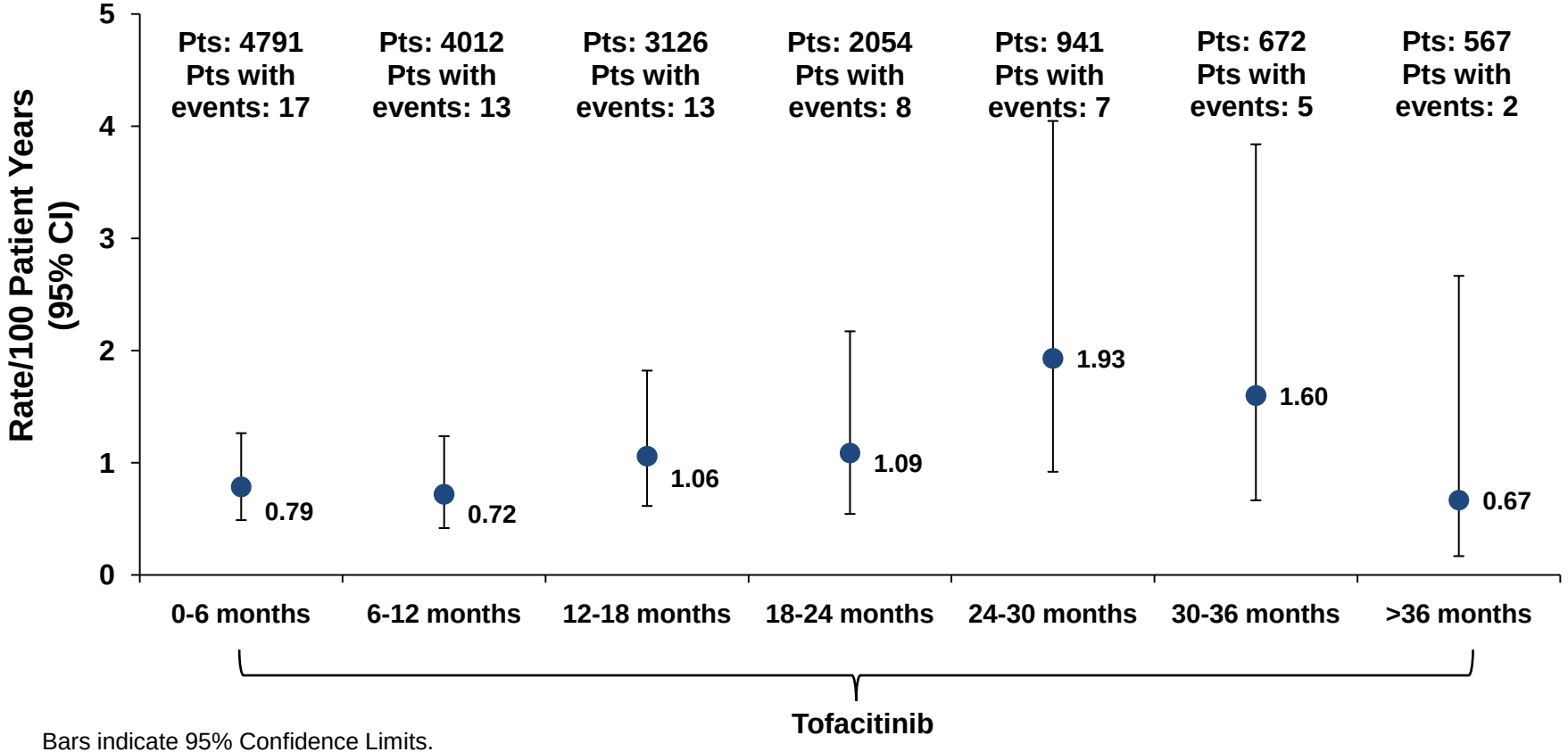

**Malignancy, excluding NMSC**
Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
*The comparator data for the standardized incidence rates (SIRs) is from observational sources primarliy due to the availability of published data.
**Data as of 29SEP2011**

# Malignancies (excluding NMSC) Rates Over Time




Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Data as of 29 September 2012

# Malignancies (excluding NMSC) Rates Over Time

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Incidence rate of patients per 100 pt-yrs
**Data as of 29 September 2011**

# Safety Topics of Special Interest

- Serious and other Important Infections
- Malignancies
  - Lymphomas
  - Lung cancer
  - Non-melanoma skin cancer
- Lipids and Cardiovascular Safety
- Hepatic Safety
- GI Perforations

# Nonclinical: Summary of Lymphomas

- Lymphoma was reported in 3/8 high dose (10 mg/kg/day) adult monkeys
  - Mechanism for B cell lymphomas in 2 monkeys is consistent with the EBV-related lymphoma in humans
  - The reported T cell lymphoma in 1 monkey could not be fully characterized due to insufficient tissue for analysis
- No lymphomas in the 39-week juvenile monkey study
- No lymphomas in the rasH2 mouse or rat carcinogenicity studies

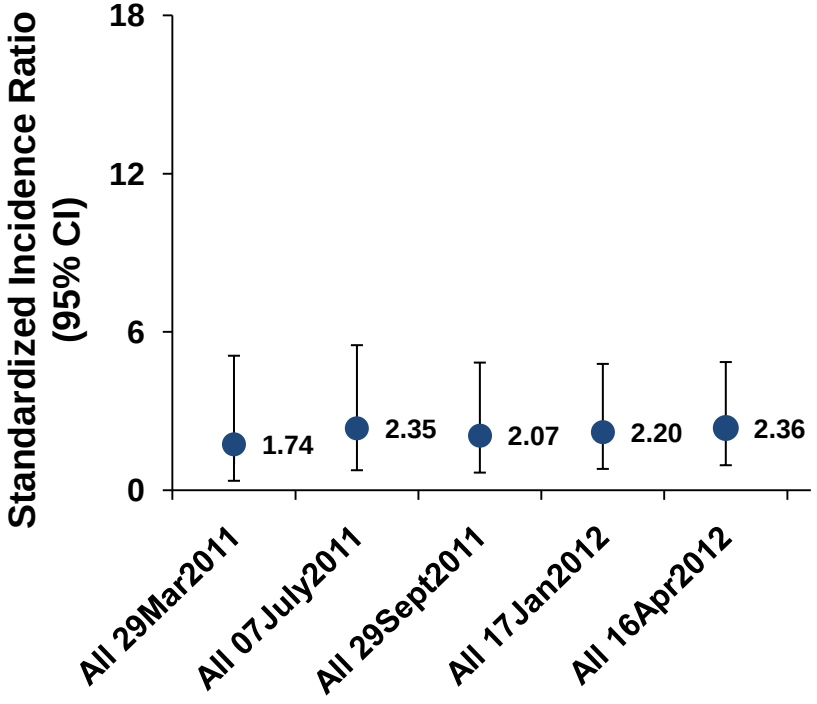
# PTLD in Tofacitinib Renal Transplant Program

- Post-transplant lymphoproliferative disorder (PTLD) is known to occur post-transplant
- Five (5) patients with PTLD were reported in tofacitinib renal transplant program out of 218 patients
  - Rate of 2.3% higher than reported rates of approximately 0.5-1%
  - All 5 occurrences were associated with Epstein-Barr virus (EBV)
  - Etiology consistent with over-immunosuppression in patients receiving tofacitinib with multiple immunosuppressive drugs including methylprednisolone, basilixumab and mycophenolate

# Lymphoma: Comparison of RA and Transplant

| Renal Transplant | Rheumatoid Arthritis |
|---|---|
| **At transplant**<br>• Immunosuppression associated with renal failure itself<br>• High dose corticosteroids (125-500 mg methylprednisolone at transplant)<br>• Basiliximab (anti-IL-2R monoclonal antibody)<br>• 15 mg BID tofacitinib<br><br>**Maintenance**<br>• Mycophenolic acid products (potent immunosuppressive)<br>• Tofacitinib dose variable | • Tofactinib monotherapy<br><br>**OR**<br><br>• Tofacitinib + DMARDs (e.g., methotrexate)<br><br>**With or without**<br>• Low dose glucocorticoids ≤ 10 mg prednisone equivalent |

# Lymphoma/LPD: Standardized Incidence Ratios Tofacitinib RA Program

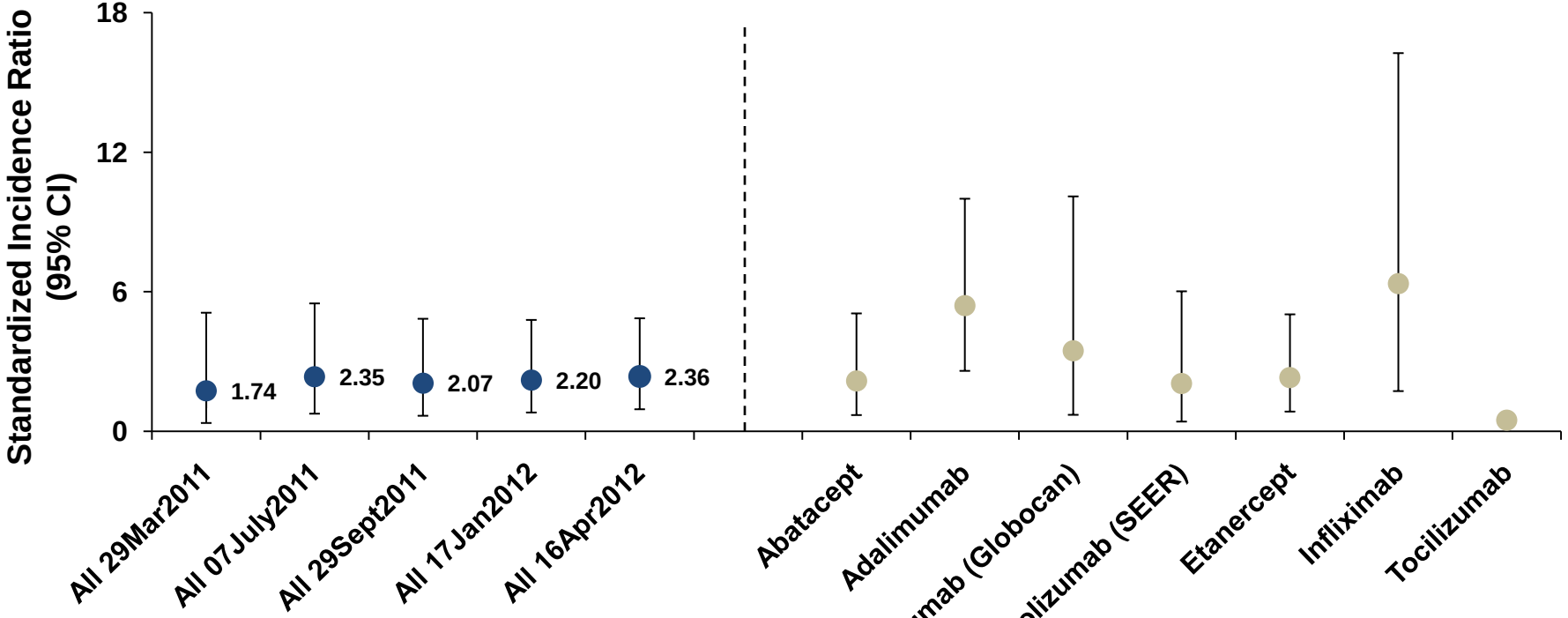



| | All Mar | All July | All Sept | All Jan | All Apr |
|---|---|---|---|---|---|
| Pts with events | 3 | 5 | 5 | 6 | 7 |
| Exposure (PY) | 5651 | 6993 | 7977 | 9071 | 9935 |

**Lymphoma SIR**
Bars indicate 95% Confidence Limits.

Incidence rate of patients per 100 pt-yrs
**Data as of 16Apr2012**

# Lymphoma/LPD: Standardized Incidence Ratios Tofacitinib RA Program

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Incidence rate of patients per 100 pt-yrs
**Data as of 16Apr2012**

# Summary of Lymphoma/Lymphoproliferative Cases in Tofacitinib RA Program

| Histology | EBV status | Demog | Onset (days) | Dose (background) | Location |
|---|---|---|---|---|---|
| Large B cell lymphoma | Neg | 78 y.o. White F | 818 | 5 mg BID (MTX) | Central Nervous System |
| Lymphoma c/w Hodgkin's | Pos | 51 y.o. Asian F | 227 | 5 mg BID | Abdominal lymph nodes |
| Low Grade B cell lymphoma | IgG:+/- and non-specific EBNA pos | 47 y.o. Asian F | 220 | 10 mg BID (MTX) | Thymus |
| Large B-cell lymphoma | EBER+ in rare, scattered mononuclear cells | 69 y.o. White F | 642 | 10 mg BID (MTX) | Left breast, media-stinum, and left axillary area |
| Large B-cell lymphoma, Burkitt-like | EBER+ in small focus of cells | 65 y.o. White M | 149 | 10 mg BID | Right submandibular gland-right neck |
| T-cell chronic lymphocytic leukemia | Neg | 63 y.o. White M | 449 | Blinded Therapy (Tofa/MTX) | Hematologic |
| Small B cell Lymphocytic Lymphoma (Mantle Cell) | Not Reported | 61 y.o. White F | 659 | 5 mg BID | Tonsil |

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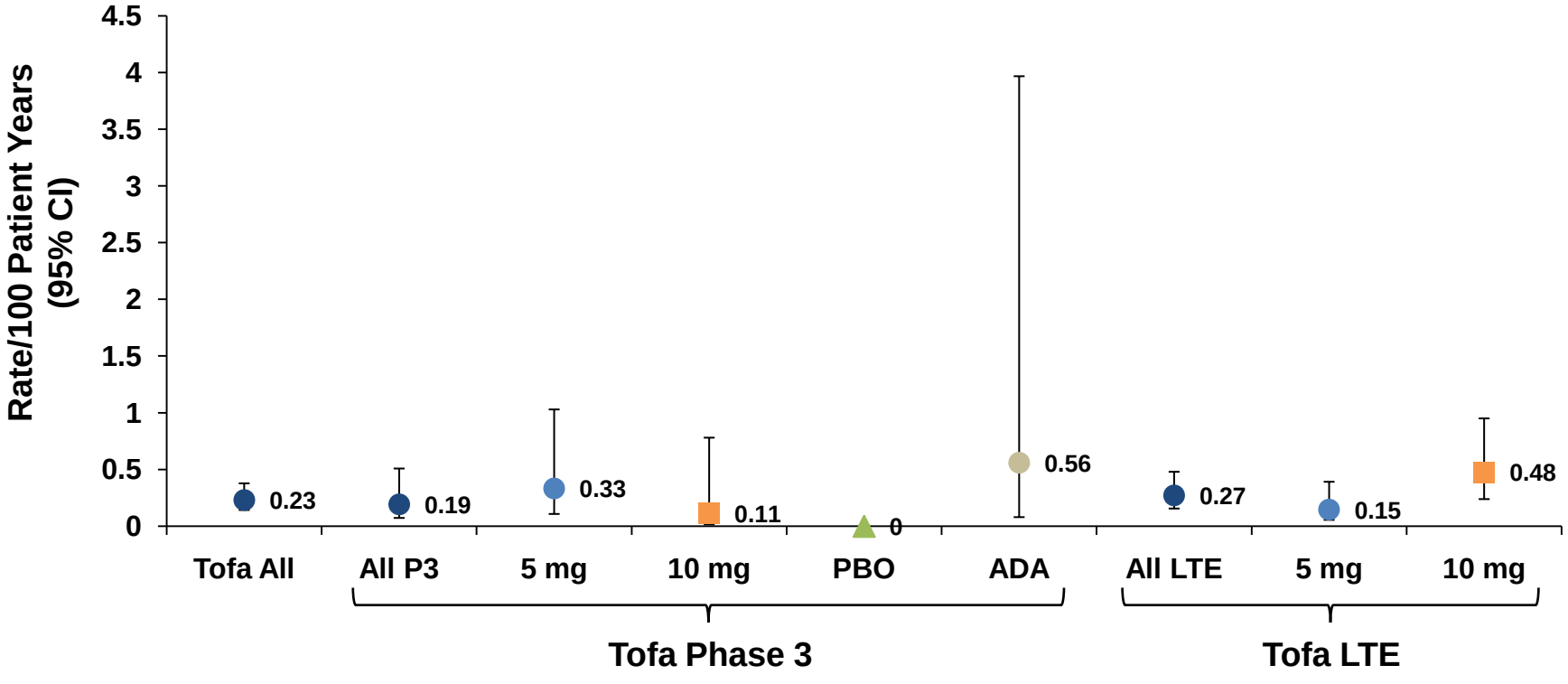
# Safety Topics of Special Interest

- Serious and other Important Infections
- Malignancies
  - Lymphomas
  - Lung cancer
  - Non-melanoma skin cancer
- Lipids and Cardiovascular Safety
- Hepatic Safety
- GI Perforations

# Lung Cancer
# Rates Consistent across Doses and Studies

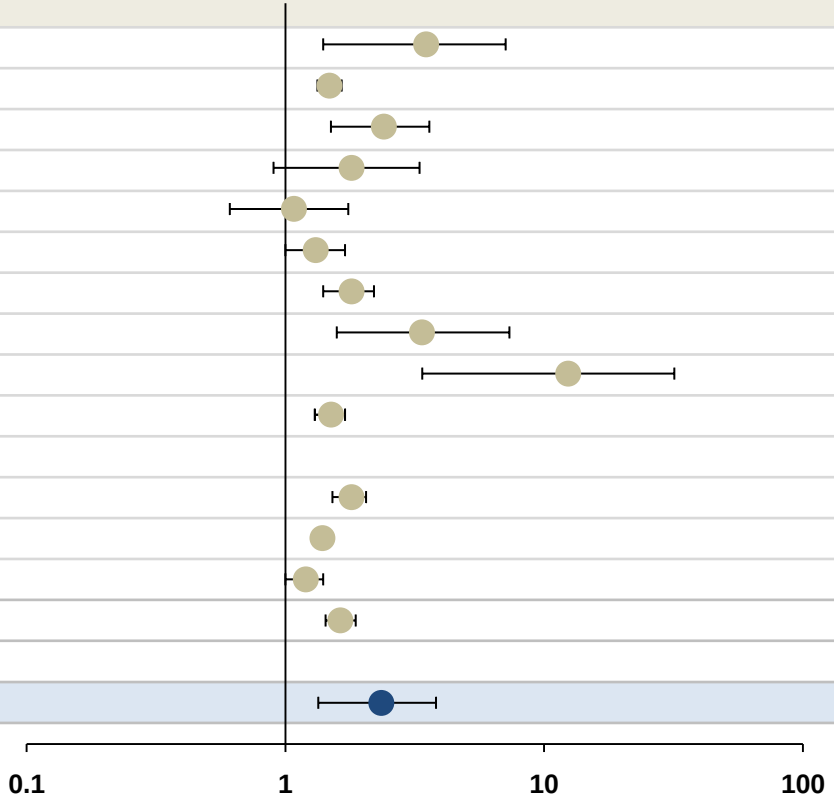



| | Tofa All | All P3 | 5 mg BID | 10 mg BID | PBO | ADA | All LTE | 5 mg BID | 10 mg BID |
|---|---|---|---|---|---|---|---|---|---|
| Pts with events | 16 | 4 | 3 | 1 | 0 | 1 | 12 | 4 | 8 |
| Exposure (PY) | 6921 | 2098 | 904 | 910 | 203 | 179 | 4409 | 2726 | 1648 |

**Data as of 29SEP2011** Incidence rate of patients per 100 pt-yrs

# Lung Cancer: Standardized Incidence Ratios

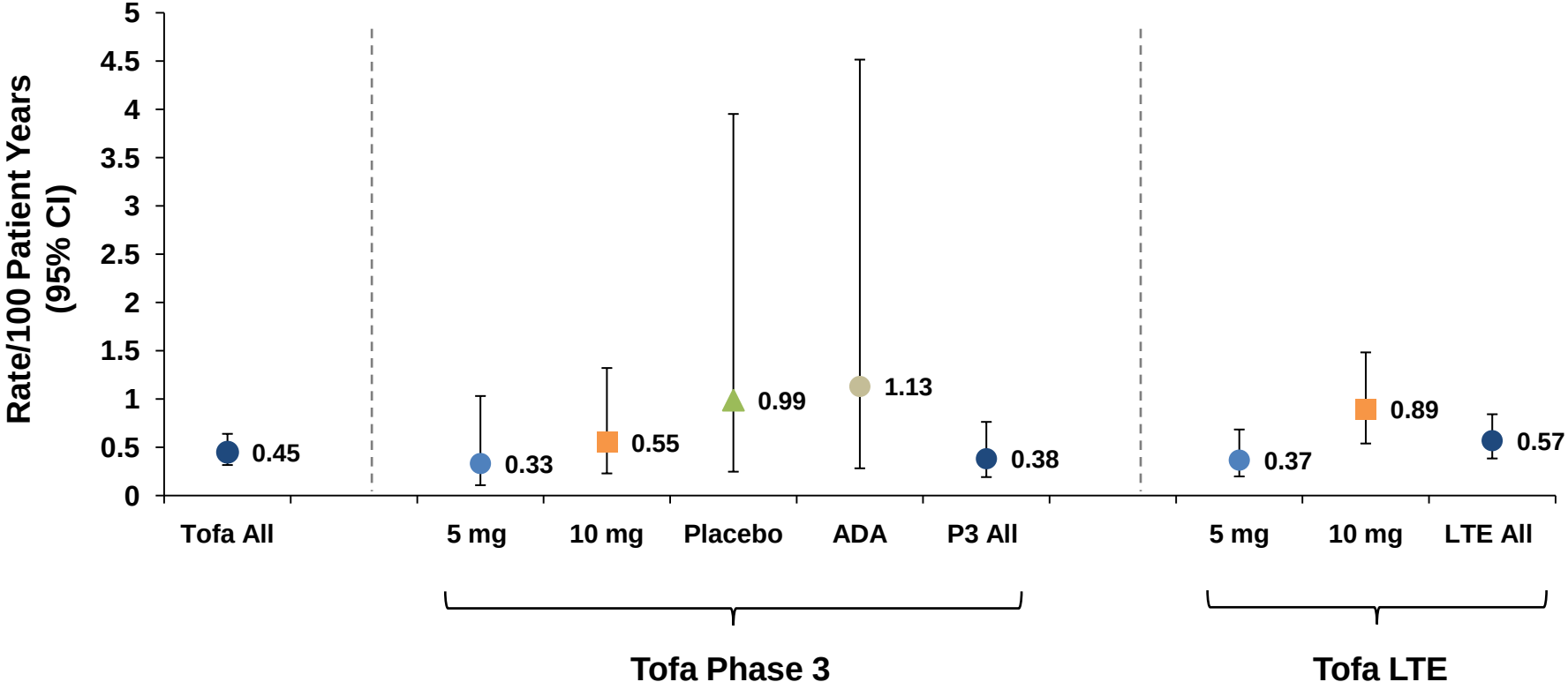
| Source | n/N | SIR (95%CI) |
|---|---|---|
| Abasolo 2007 | 7/789 | 3.5 (1.40, 7.10) |
| Askling 2005 | 330/53067 | 1.48 (1.33, 1.65) |
| Askling 2005 (early RA) | 23/3703 | 2.4 (1.50, 3.60) |
| Askling 2005 (anti-TNF) | 10/4160 | 1.8 (0.90, 3.30) |
| Cibere 1997 | 16/862 | 1.08 (0.61, 1.75) |
| Gridley 1993 | 68/11683 | 1.31 (1.00, 1.70) |
| Kauppi 1996 | 73/8920 | 1.8 (1.40, 2.20) |
| Matteson 1991 (DMARDs) | 6/530 | 3.37 (1.58, 7.34) |
| McKendry 1993 (MTX) | 4/144 | 12.4 (3.38, 31.84) |
| Mellemkjaer 1996 | 308/20669 | 1.5 (1.30, 1.70) |
| Moritomo 1995 | 0/655 | 0 (0.00, 1.82) |
| Setoguchi2006 | 169/7830 | 1.8 (1.52, 2.05) |
| Thomas 2000 | 472/26623 | 1.39 (1.30, 1.50) |
| Wolfe2007 | 112/13869 | 1.2 (1.00, 1.40) |
| Smitten, 2008 (Overall) | NAV | 1.63 (1.43, 1.87) |
| Tofacitinib | 16/4791 | 2.35 (1.34, 3.82) |




Smitten AL, et al., A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Research & Therapy 2008; 10: R45. Note: SEER data were used as the comparator for the tofacitinib SIRs.

**Data as of 29SEP2011** Incidence rate of patients per 100 pt-yrs

# Nonmelanoma Skin Cancers
# Incidence Rates Consistent Across Dose Groups




Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
**Data as of 29 September 2012**

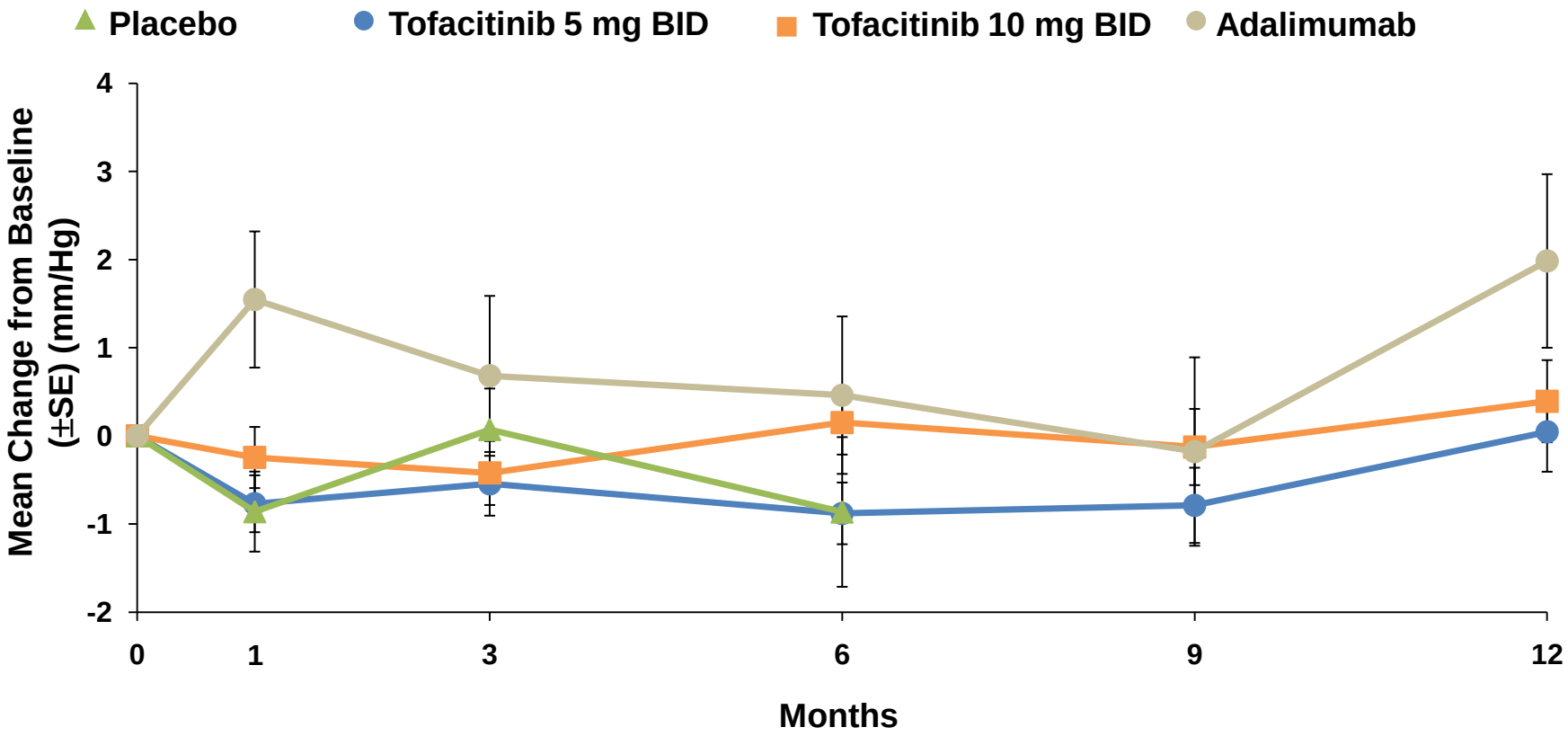
# Risk Assessment/Mitigation: Malignancies

| Risk Assessment | |
|---|---|
| **Clinical/Observational Studies** | **Assessment** |
| Ongoing (including LTE) and future clinical studies | • Incidence rates<br>• Type/nature<br>• Histopathology over-read (central laboratory) |
| CORRONA<br>EU Registries | Incidence rates of malignancies among users of tofacitinib |
| **Risk Mitigation** | |
| Warnings and Precautions | • Tofacitinib may affect host defenses against malignancies |
| Medication Guide for Patients | • Tofacitinib, like other medicines that affect the immune system, may increase your risk of certain cancers. |

# Safety Topics of Special Interest

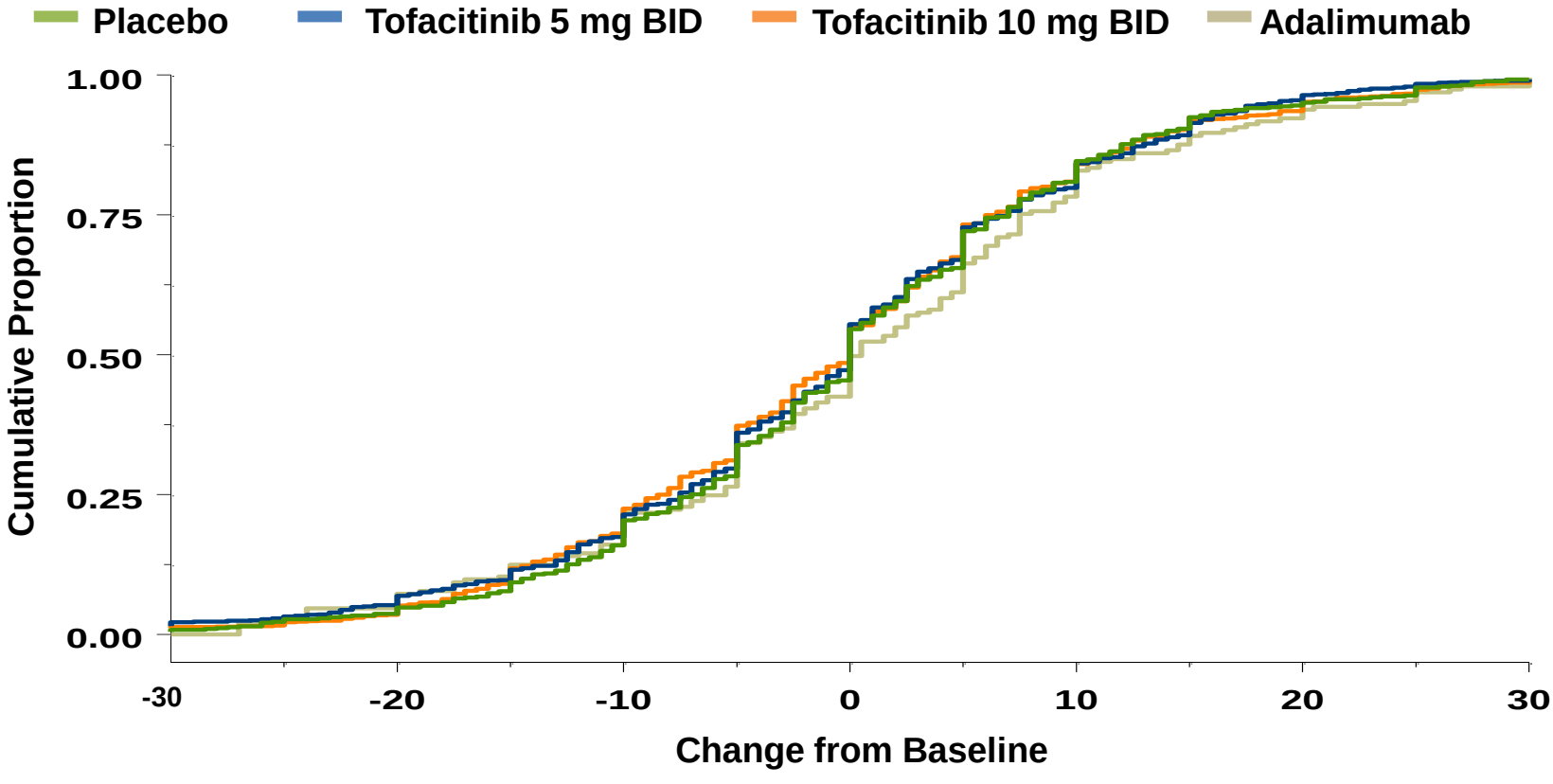
- Serious and other Important Infections
- Malignancies
- Lipids and Cardiovascular Safety
  - Blood pressure
  - Lipids
  - CV Events
- Hepatic Safety
- GI Perforations

# Systolic Blood Pressure
# Mean Changes over Time

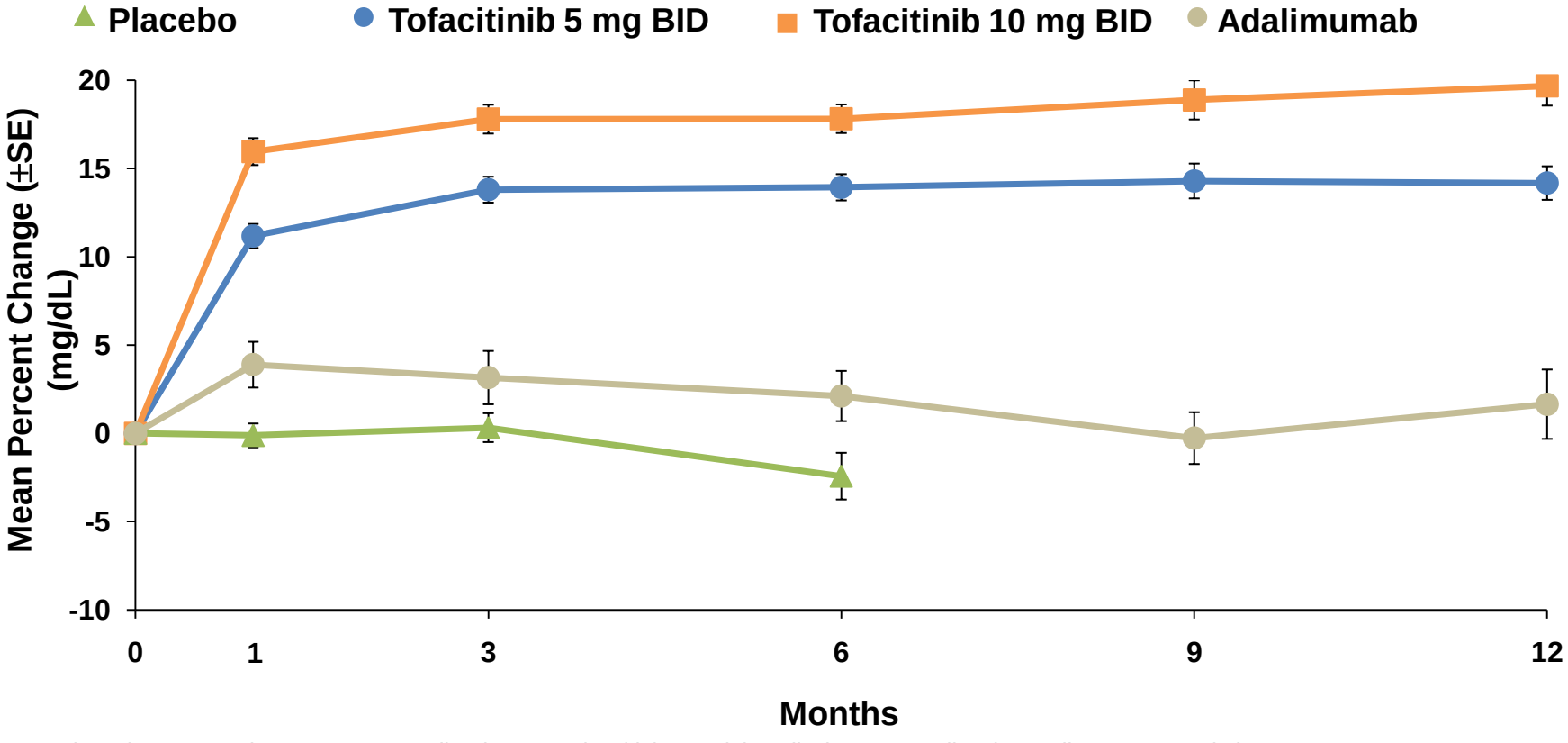



Mean (± SE) Change From Baseline Systolic Blood Pressure (mm Hg) per Visit in All Phase 3 Studies (0 to 12 Months)
**Data as of 29 March 2011**

# Change in Systolic Blood Pressure Similar Across Treatment Groups



# Increases in LDL-c with Tofacitinib Treatment




Mean (± SE) Percent Change From Baseline in LDL-c (mg/dL) per Visit - All Phase 3 Studies (Overall 0 to 12 Months)
**Data as of 29 March 2011**

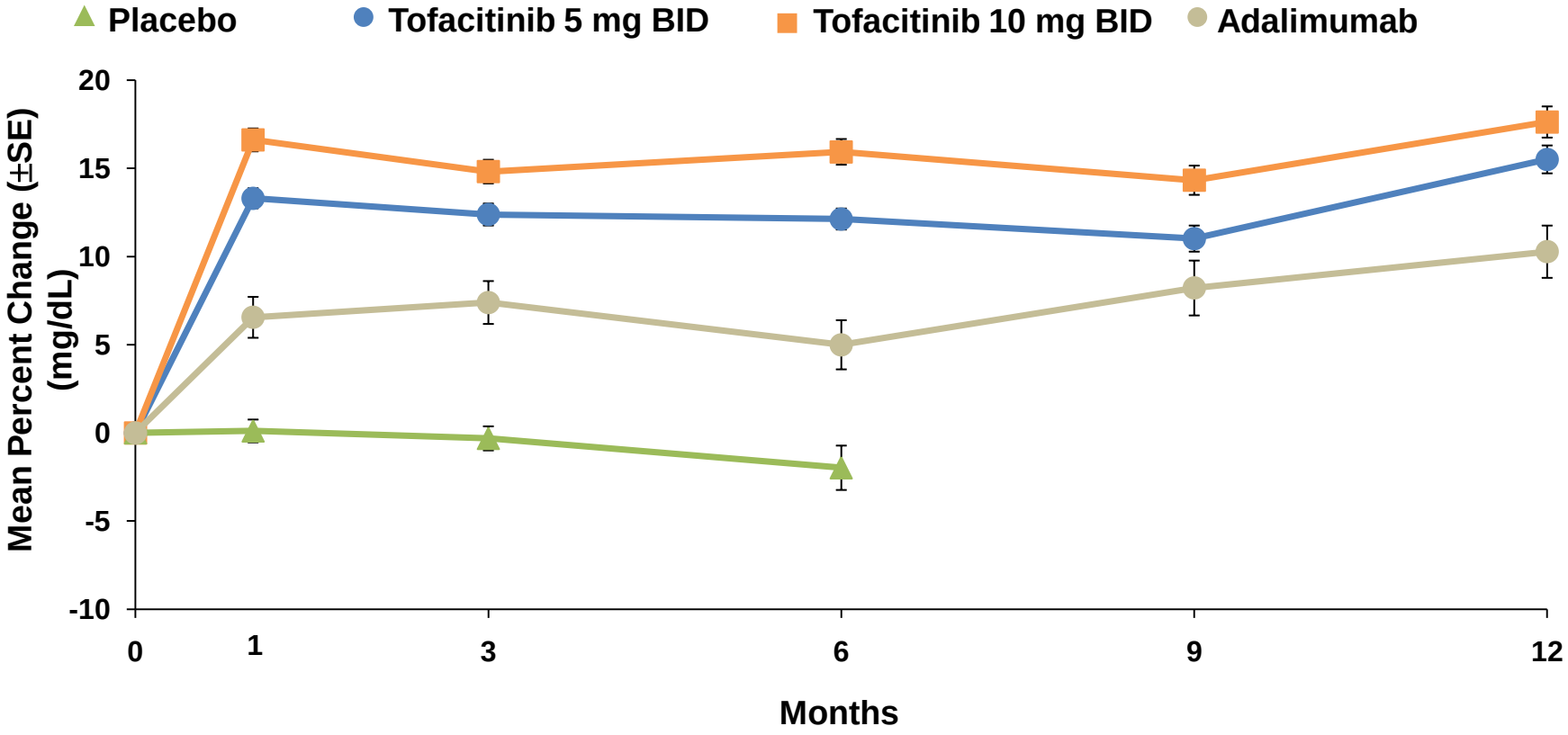
# LDL-c Shift: Maximum On-Treatment Levels

| | Maximum on-Treatment Cholesterol LDL (mg/dL) (Phase 3, 0-3 Months) n (%)* | | | | | |
|---|---|---|---|---|---|---|
| Baseline (mg/dL) | <100 | 100 to <130 | 130 to <160 | 160 to <190 | ≥190 | Total |
| <100 | 404 (45) | 349 (39) | 118 (13) | 20 (2) | 6 (0.7) | 897 (100) |
| 100 to <130 | 31 (4) | 267 (35) | 328 (43) | 104 (14) | 26 (3) | 756 (100) |
| 130 to <160 | 6 (1) | 35 (7) | 200 (41) | 179 (37) | 65 (13) | 485 (100) |
| 160 to <190 | 1 (0.6) | 2 (1) | 24 (15) | 65 (39) | 73 (44) | 165 (100) |
| ≥190 | 0 (0.0) | 1 (2) | 2 (3) | 6 (10) | 53 (85) | 62 (100) |
| Total | 442 (19) | 654 (28) | 672 (28) | 374 (16) | 223 (9) | 2365 (100) |

Only subjects with both a valid baseline and an on-treatment value for the parameter of interest are included in the table
* For each baseline category

**Data as of 29-Mar-2011**

# Increases in HDL-c with Tofacitinib Treatment

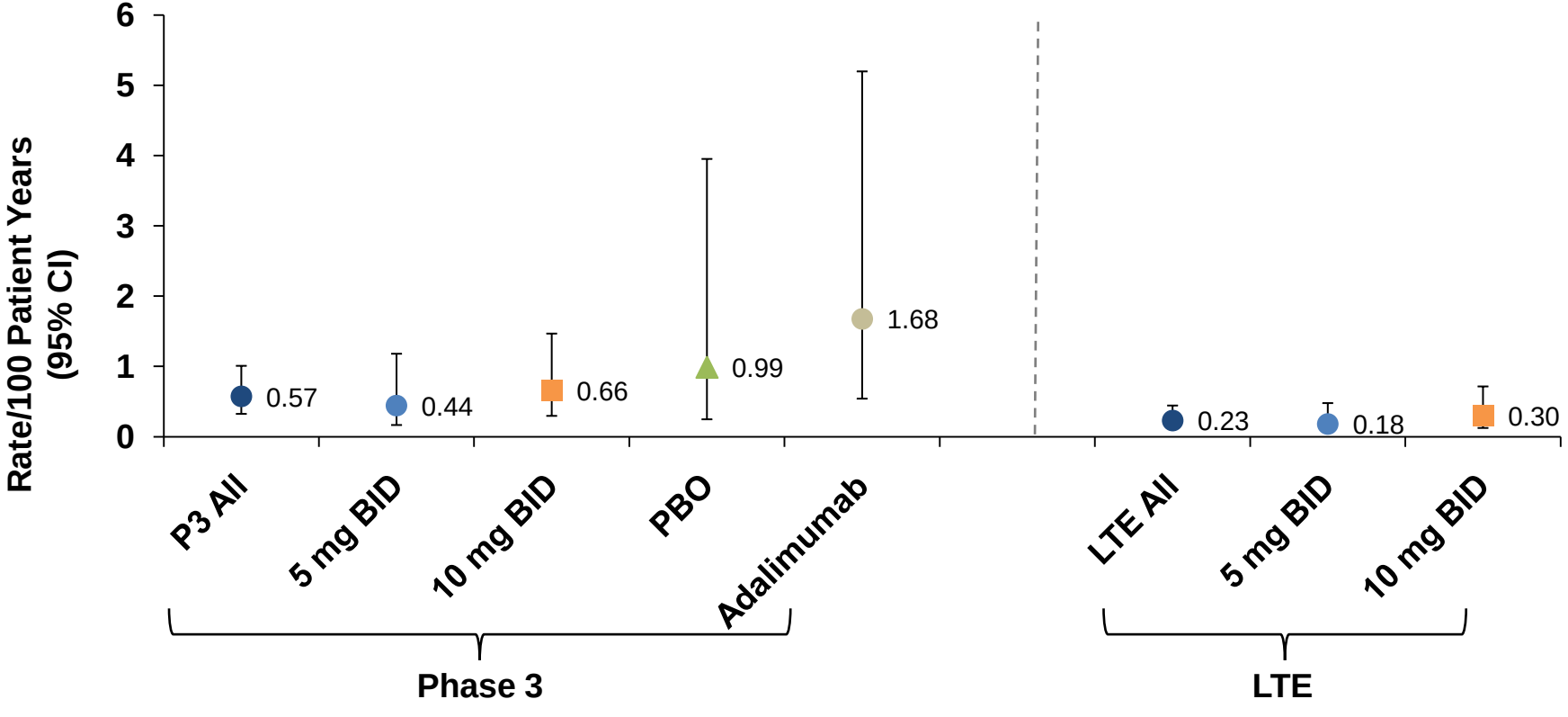



Mean (± SE) Percent Change From Baseline in HDL-c (mg/dL) per Visit in Phase 3 Studies (Overall 0 to 12 Months)
**Data as of 29 March 2011**

# Adjudicated Cardiovascular Events

- Adjudicated by external, blinded committee using pre-specified criteria
  - Major adverse cardiovascular events (MACE)
  - Myocardial infarction
  - Cerebrovascular events
  - Congestive heart failure
- Rates of CV events were low and similar to TNF inhibitors and other biologics
- Rates remained low in long-term extension studies
  - No accumulation of risk over time

# MACE: Incidence Rates Across Dose Groups




| | All P3 | 5 mg BID | 10 mg BID | PBO | ADA |
|---|---|---|---|---|---|
| Pts with events | 12 | 4 | 6 | 2 | 3 |
| Exposure (PY) | 2098 | 903 | 910 | 202 | 179 |

Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
Data as of 29 September 2012

# Risk Assessment: Lipids and CV Safety

| Clinical/Observational Studies | Assessment |
|---|---|
| Cholesterol kinetic study | • Assess kinetics of cholesterol flux through the HDL/reverse cholesterol transport pathway<br>• RA patients and healthy volunteers |
| CORRONA<br><br>CORRONA and EU Registries | • Cohort study assessing CV risk<br><br>• Active surveillance of CV events including: major adverse cardiovascular events, MI, CVA/stroke, congestive heart failure, etc. |

# Risk Mitigation: Lipids and CV Safety

| | |
|---|---|
| **Warning and Precautions** | • Assess Lipids 4-8 weeks after tofacitinib initiation<br>• Manage hyperlipidemia according to clinical guidelines |

- Tofacitinib therapy is associated with increases in LDL-c and HDL-c
- No imbalance has been observed on CV event rates
- LDL-c increases respond to statin therapy

# Safety Topics of Special Interest

- Serious and other Important Infections
- Malignancies
- Lipids and Cardiovascular Safety
- Hepatic Safety
- GI Perforations

# Hepatic Safety
# Transaminase Elevations

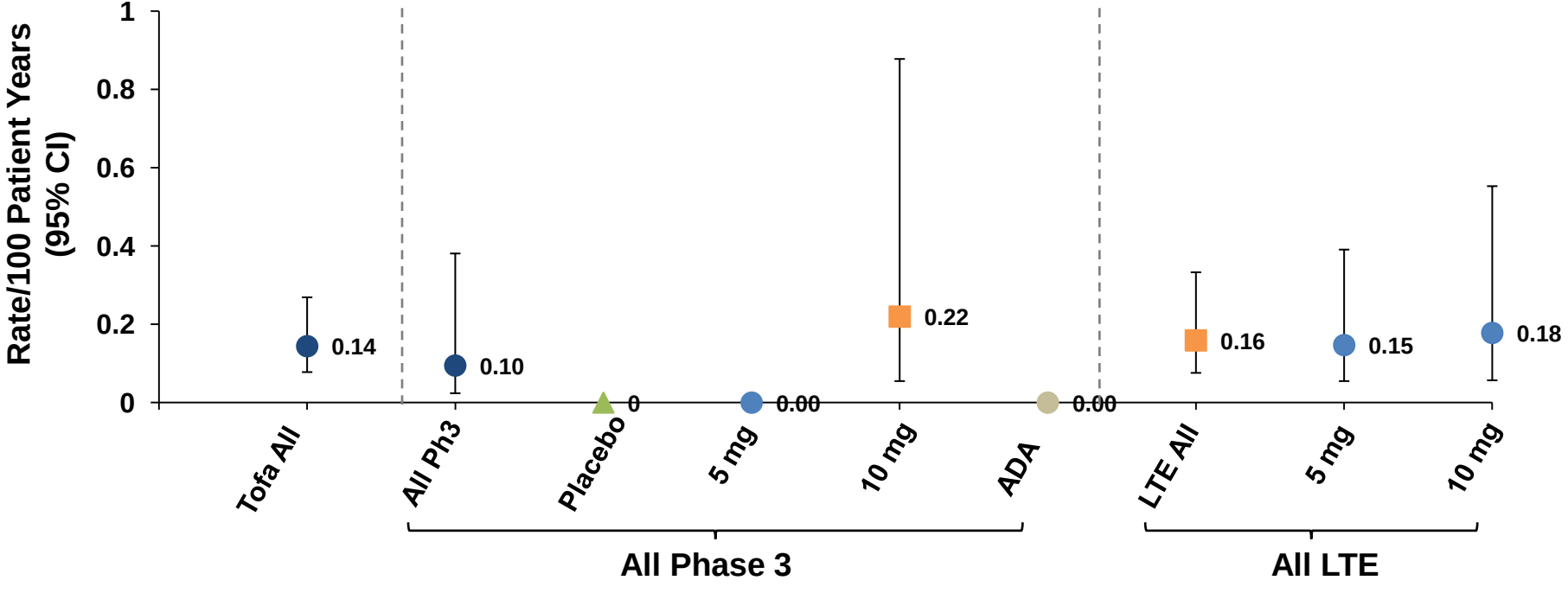
| 0 to 3 Months | Tofacitinib 5 mg BID N=968 | Tofacitinib 10 mg BID N=962 | Placebo N=554 | Adalimumab 40 mg q2w N=204 |
|---|---|---|---|---|
| **Phase 3 DMARD Studies** | | | | |
| AST | | | | |
| ≥1 x ULN | 166 (17) | 187 (19) | 54 (10) | 25 (12) |
| ≥3 x ULN | 3 (0.3) | 2 (0.2) | 2 (0.4) | 0 |
| ALT | | | | |
| ≥1 x ULN | 172 (18) | 204 (21) | 67 (12) | 32 (16) |
| ≥3 x ULN | 5 (0.5) | 7 (0.7) | 0 | 0 |
| **Phase 3 Monotherapy Study** | | | | |
| AST | | | | |
| ≥1 x ULN | 23 (9) | 29 (12) | 7 (6) | |
| ≥3 x ULN | 1 (0.4) | 0 | 1 (0.8) | |
| ALT | | | | |
| ≥1 x ULN | 23 (9) | 28 (11) | 11 (9) | |
| ≥3 x ULN | 1 (0.4) | 0 | 1 (0.8) | |

Data as of 29Mar2011

# Hepatic Safety
# Concurrent Elevations in ALT/AST and Bilirubin

- Six (6) patients with ALT/AST > 3X ULN and Bilirubin >2X ULN
  - Five (5) not consistent with Drug-induced Liver Injury due to alternative diagnoses and/or alkaline phosphatase >2X ULN
- One (1) patient with possible Drug-Induced Liver Injury
  - Patient with asymptomatic transaminitis while on study, and a concomitant increased bilirubin 2-3 months after discontinuation of tofacitinib
  - Liver tests responded to prednisolone and azathioprine, suggestive of possible autoimmune hepatitis
  - However drug-induced liver injury could not be ruled out

# Gastrointestinal Perforations Rates Across Dose Groups




| | Tofa All | All P3 | 5 mg BID | 10 mg BID | All LTE | 5 mg BID | 10 mg BID |
|---|---|---|---|---|---|---|---|
| Pts with events | 10 | 2 | 0 | 2 | 7 | 4 | 3 |
| Exposure (PY) | 6921 | 2098 | 904 | 910 | 4409 | 2726 | 1684 |

Bars indicate 95% Confidence Limits.
Incidence rate of patients per 100 pt-yrs
**Data as of 29 September 2012**

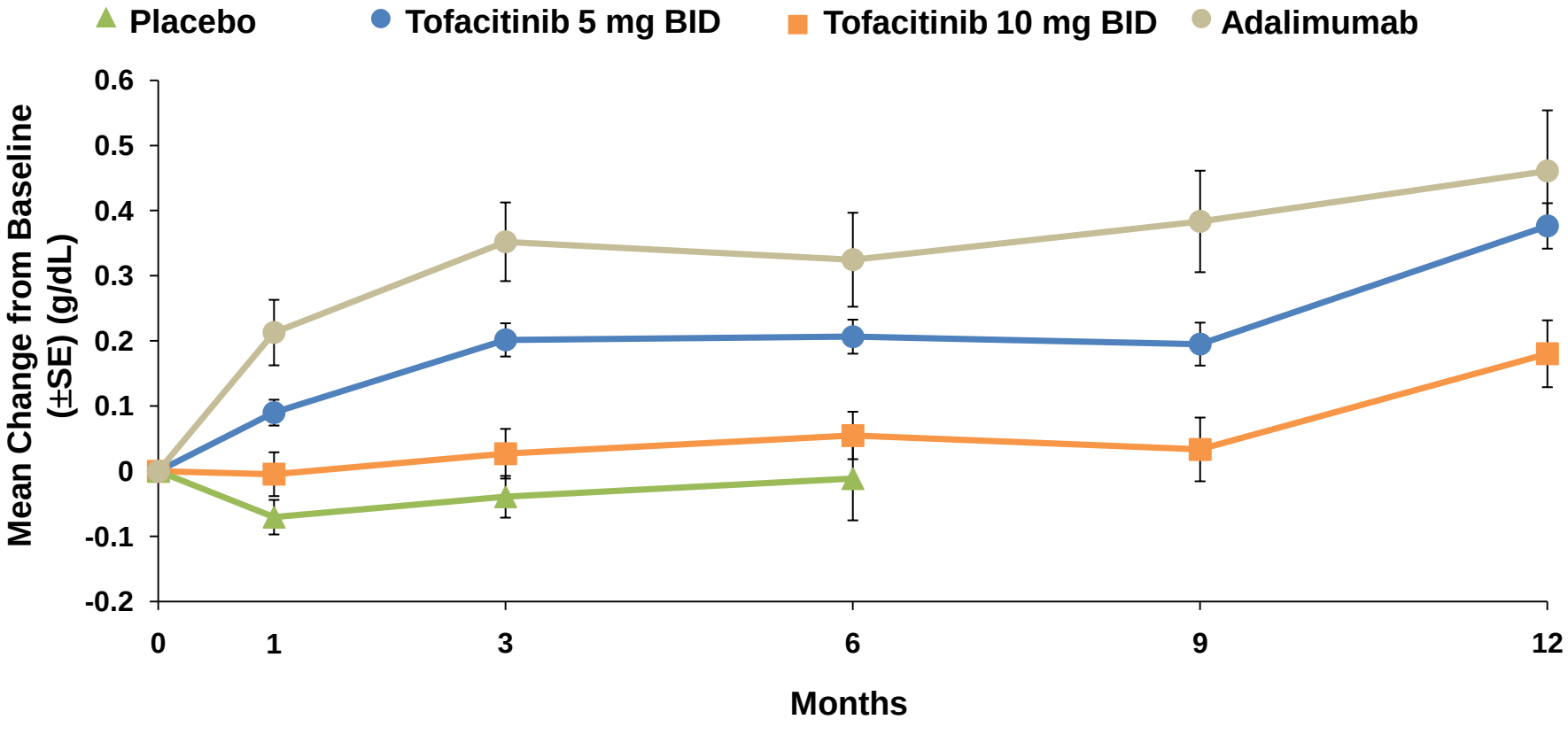
# Risk Assessment:
# Hepatic Safety and GI Perforations

| Risk Assessment | |
|---|---|
| **Clinical/Observational Studies** | **Assessment** |
| Ongoing (including LTE) and future clinical studies | • Planned adjudication of important hepatic events<br>• Incidence rates of gastrointestinal perforations |
| CORRONA<br>EU Registries | •Incidence rates of events of interest among users of tofacitinib |
| **Risk Mitigation** | |
| Warnings and Precautions | •Gastrointestinal Perforations – Use with caution in patients that may be at increased risk. |

# Laboratory Changes

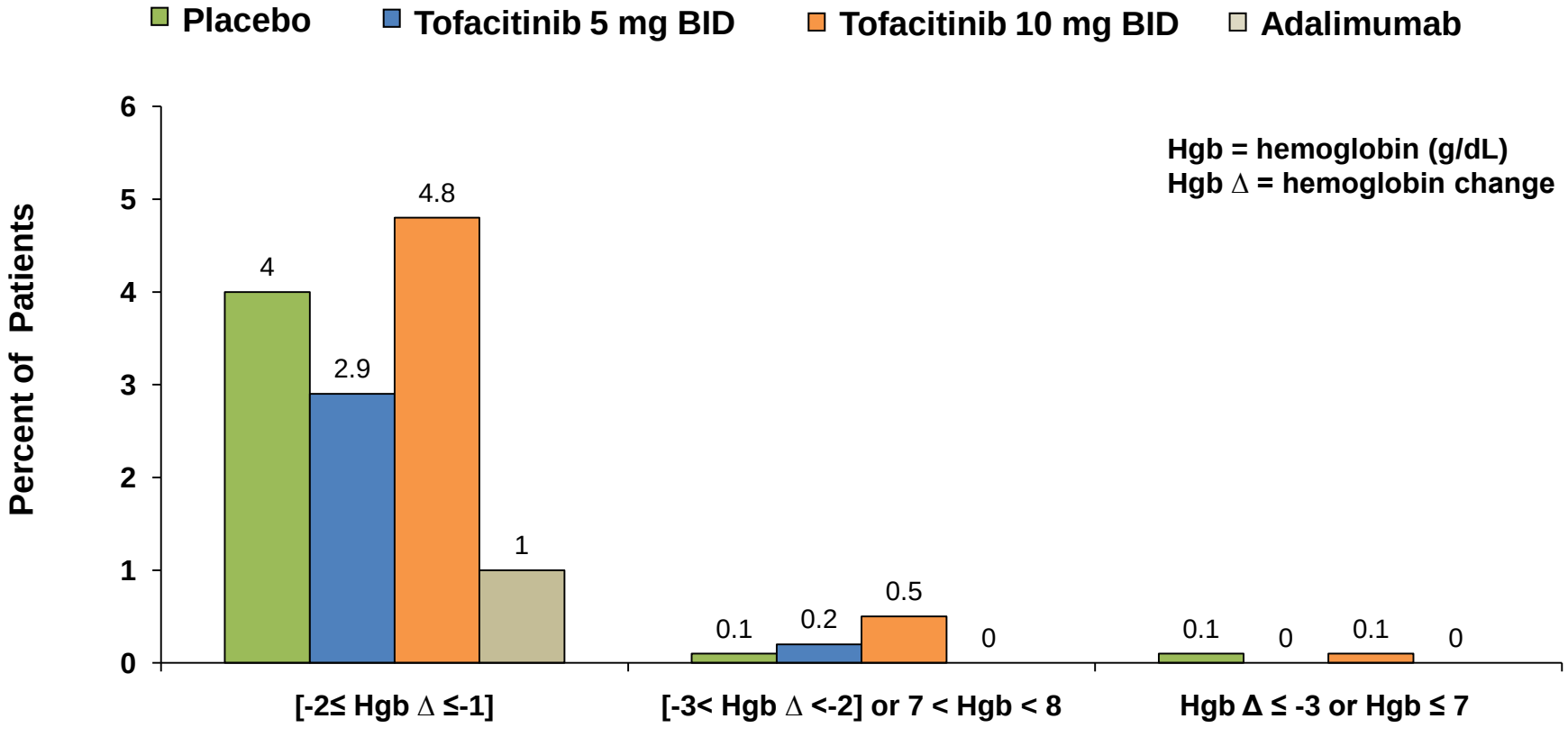
- Hemoglobin
- Neutrophils
- Lymphocytes
- Creatinine

# Hemoglobin
# Mean Increases with 5 mg



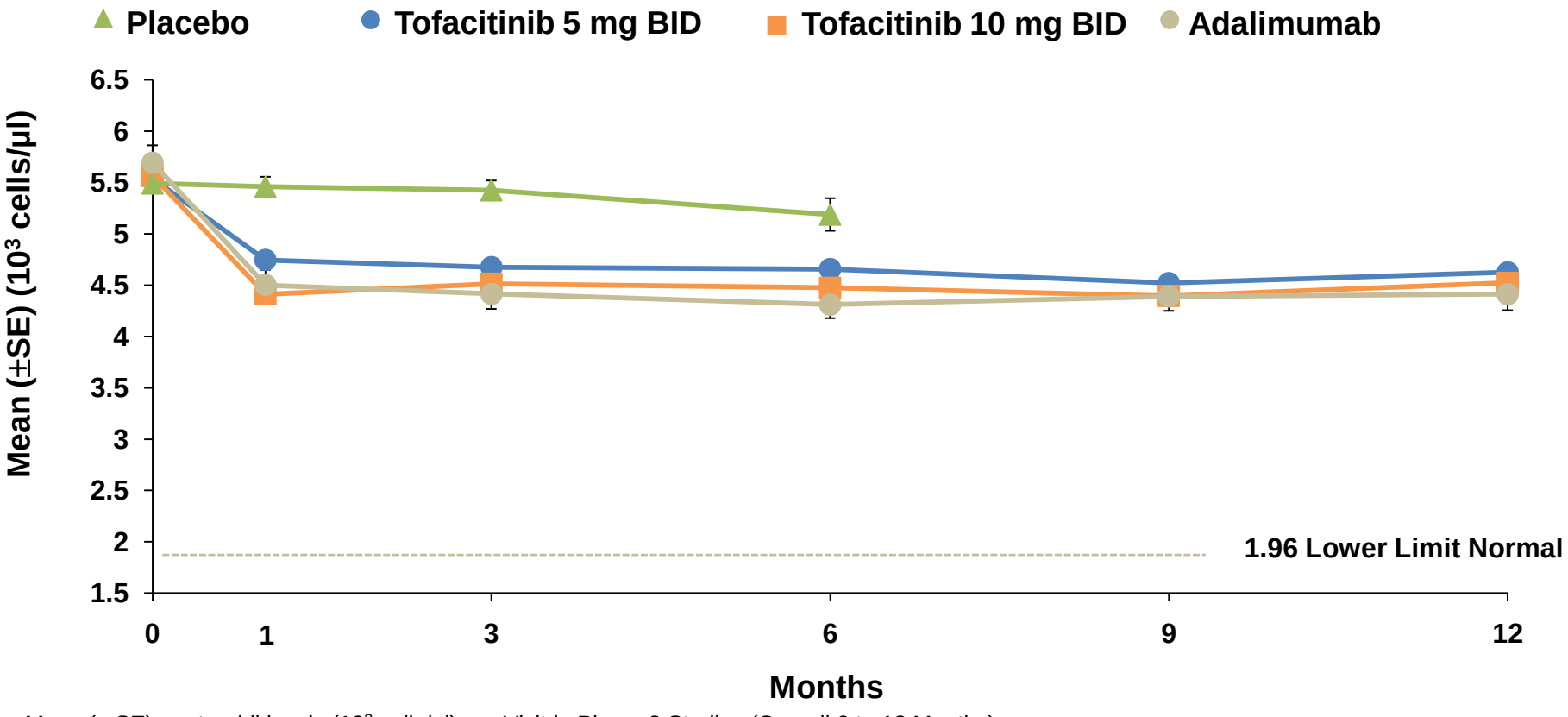

Mean (± SE) Percent Change From Baseline in hemoglobin (g/dL) per Visit in Phase 3 Studies (Overall 0 to 12 Months)
**Data as of 29 March 2011**

# Confirmed Hemoglobin Decreases
# Phase 3 Controlled Studies (0-3 months)



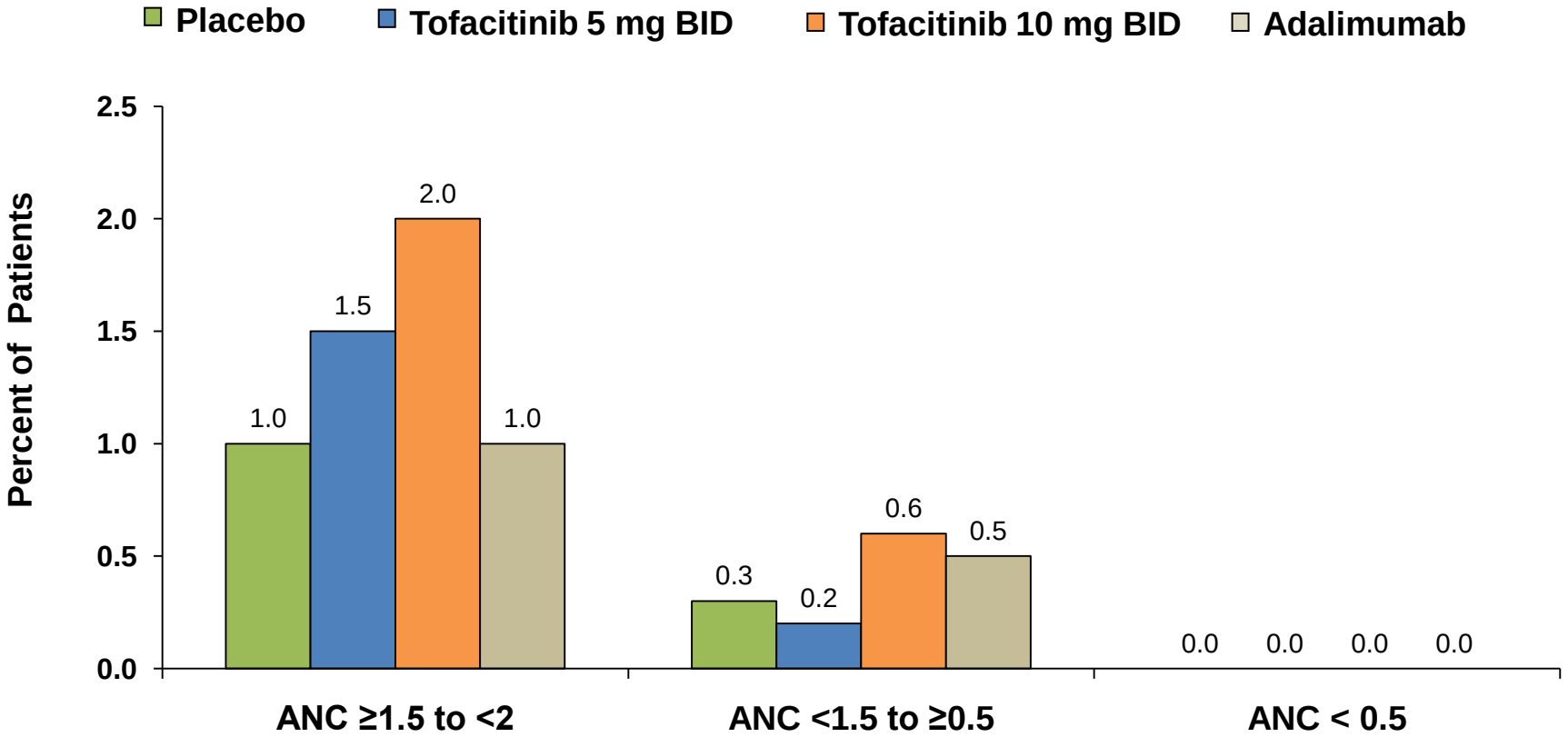

Data as of 29 March 2011

# Neutrophils
# Dose Dependent Decreases Consistent with Adalimumab




Mean (± SE) neutrophil levels ($10^3$ cells/µl) per Visit in Phase 3 Studies (Overall 0 to 12 Months)
**Data as of 29 March 2011**

# Confirmed Neutropenia
# Phase 3 Controlled Studies (0-3 months)

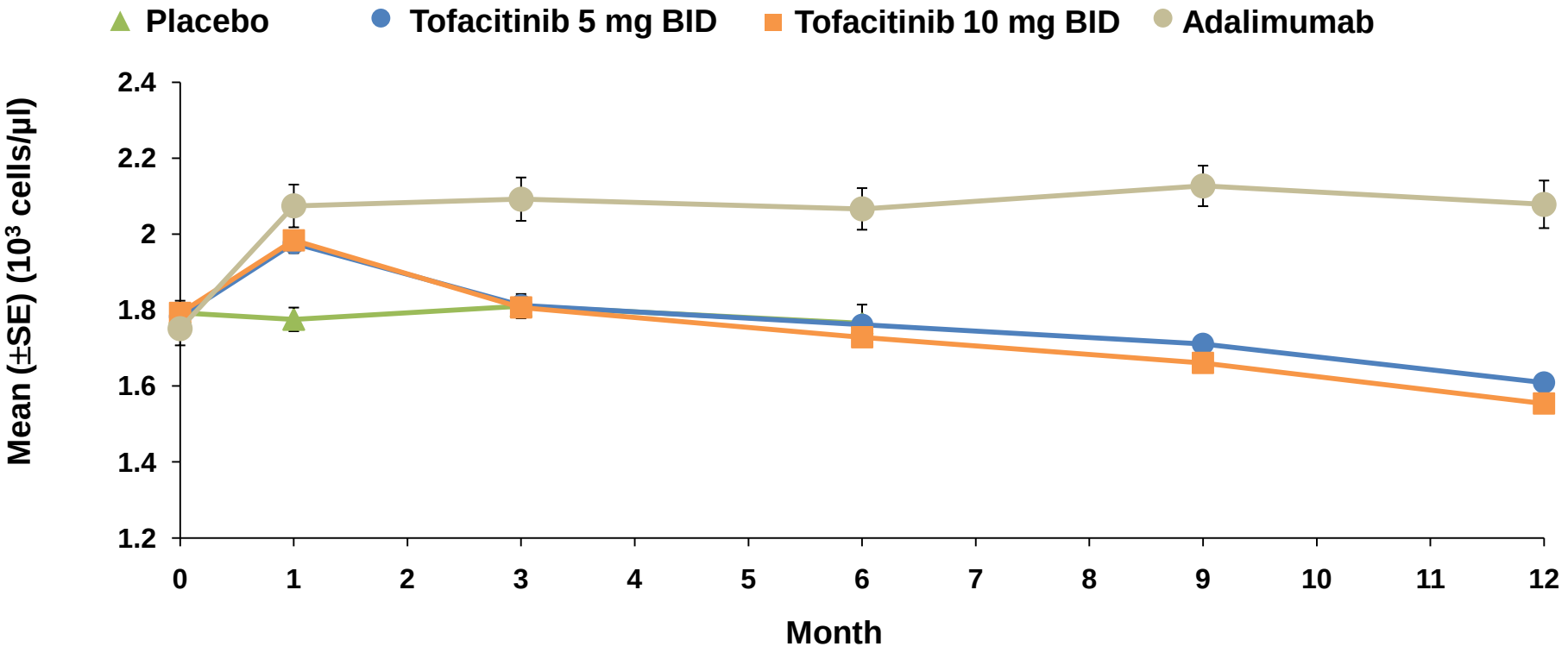



ANC = absolute neutrophil count (x1000 cells/mm$^3$)
**Data as of 29 March 2011**

# Risk Mitigation: Hemoglobin and Neutrophils

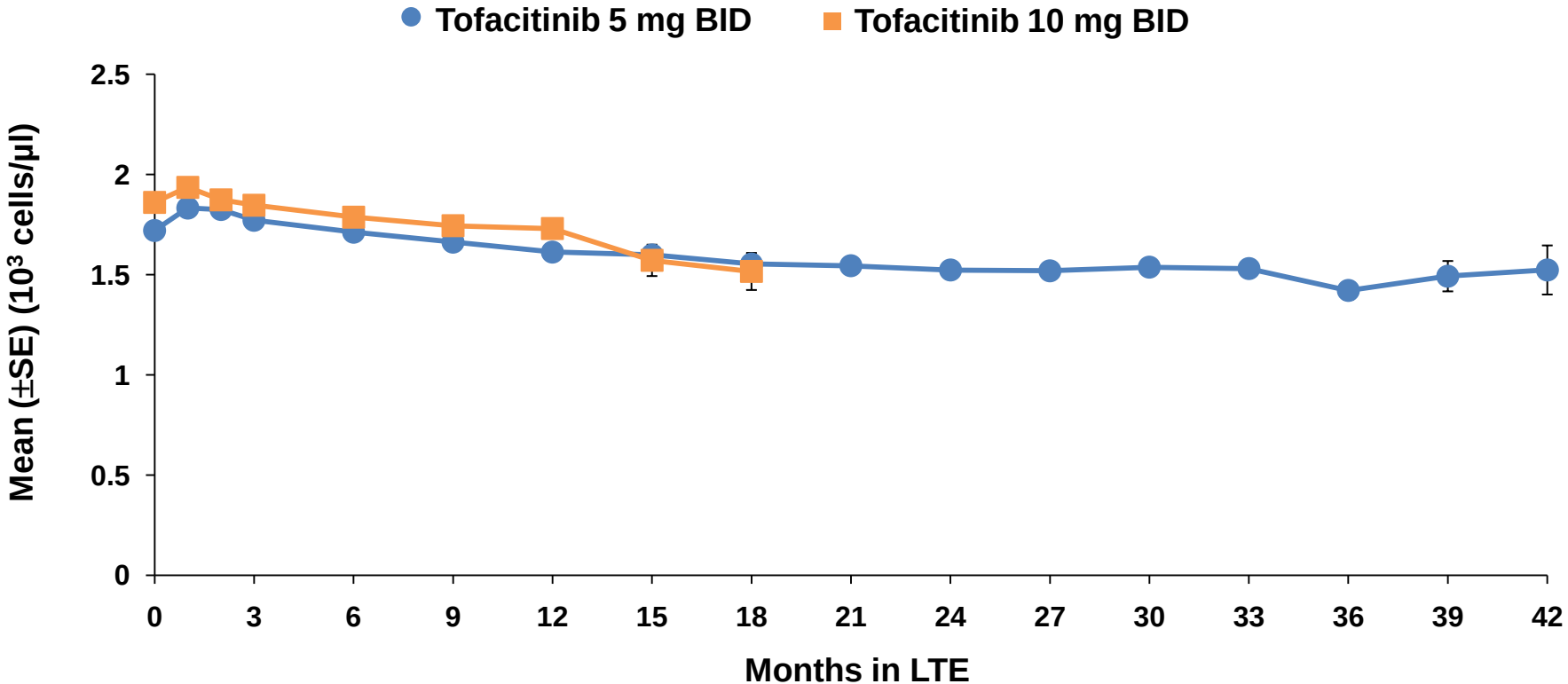
| **Hemoglobin** | |
|---|---|
| Dosage Modification | Monitor at baseline, 4-8 weeks after initiation of therapy and every 3 months thereafter |
| Warnings and Precautions | • Do not initiate tofacitinib for level of <9 g/dL<br>• Reduce or interrupt dose for confirmed level of <8 g/dL or a >2 g/dL decrease |
| **Neutrophils** | |
| Dosage Modification | Monitor at baseline, 4-8 weeks after initiation of therapy and every 3 months thereafter |
| Warnings and Precautions | • Do not initiate tofacitinib for level of <1000/$mm^3$<br>• Reduce or interrupt dose for persistent level of 500-1000/$mm^3$<br>• Discontinue for confirmed level of <500/$mm^3$ |

# Lymphocytes
# Mean Values Over Time in Phase 3




Mean (± SE) lymphocyte levels ($10^3$ cells/µl) per Visit in Phase 3 Studies (Overall 0 to 12 Months), **Data as of 29 March 2011**

# Lymphocytes
# Mean Values Over Time in LTE




| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5mg N=1262 | 1282 | 1258 | 1244 | 1073 | 1020 | 923 | 815 | 739 | 682 | 659 | 625 | 448 | 284 | 125 | 55 | 30 |
| 10mg N=1780 | 1809 | 1694 | 1528 | 933 | 541 | 246 | 78 | 30 | | | | | | | | |

Mean (± SE) lymphocyte levels ($10^3$ cells/µl) per Visit in LTE Studies (Overall), **Data as of 29 March 2011**

# Lymphopenia and Serious Infections: LTE

## Higher Incidence for Confirmed Lymphopenia of <500/mm$^3$

| Confirmed Lymphopenia | Tofacitinib 5 mg BID | | Tofacitinib 10 mg BID | | Tofacitinib All Doses | |
|---|---|---|---|---|---|---|
| | N* | n$^{\Psi}$ (%) | N* | n$^{\Psi}$ (%) | N* | n$^{\Psi}$ (%) |
| None | 222 | 8 (3.6) | 819 | 19 (2.3) | 1041 | 27 (2.6) |
| Lymphocyte Count$^{\dagger}$: | | | | | | |
| ≥1.5 to <2 | 318 | 10 (3.1) | 486 | 9 (1.9) | 804 | 19 (2.4) |
| <1.5 to ≥ 0.5 | 773 | 30 (3.9) | 591 | 13 (2.2) | 1364 | 43 (3.2) |
| <0.5 | 6 | 2 (33) | 4 | 2 (50) | 10 | 4 (40) |

*N = total number of patients in a Lymphocyte category
$^{\Psi}$n = the number of patients in that category with serious infection
$^{\dagger}$ Lymphocytes reported as x10**3/mm3

Data as of 29 March 2011

# Lymphopenia and Serious Infections: LTE

## Higher Incidence for Confirmed Lymphopenia of <500/mm$^3$

| Confirmed Lymphopenia | Tofacitinib 5 mg BID | | Tofacitinib 10 mg BID | | Tofacitinib All Doses | |
|---|---|---|---|---|---|---|
| | N* | n$^{\Psi}$ (%) | N* | n$^{\Psi}$ (%) | N* | n$^{\Psi}$ (%) |
| None | 222 | 8 (3.6) | 819 | 19 (2.3) | 1041 | 27 (2.6) |
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Data as of 29 March 2011

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| | N* | n$^{\Psi}$ (%) | N* | n$^{\Psi}$ (%) | N* | n$^{\Psi}$ (%) |
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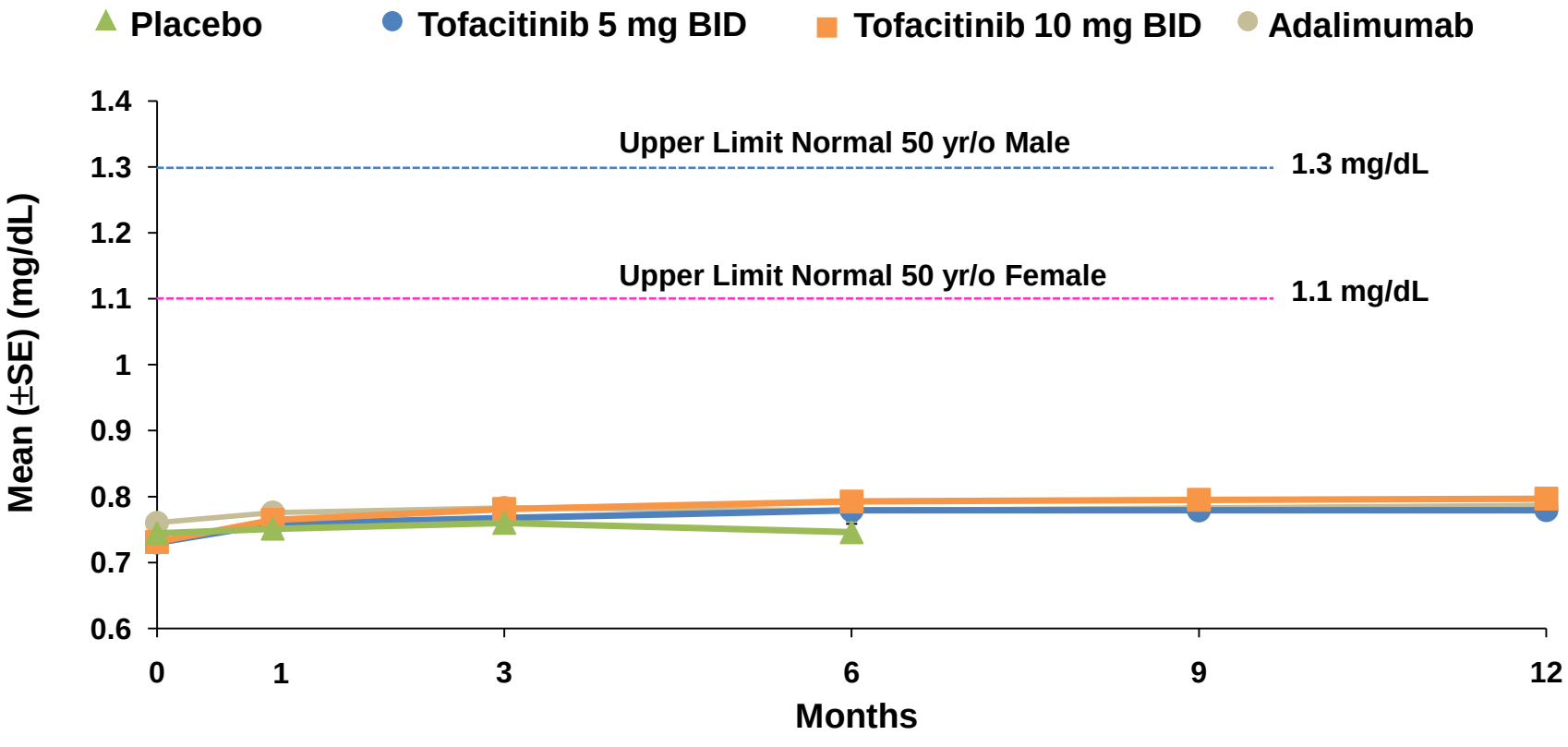
*N = total number of patients in a Lymphocyte category
$^{\Psi}$n = the number of patients in that category with serious infection
$^{\dagger}$ Lymphocytes reported as x10**3/mm3

Data as of 29 March 2011

# Risk Mitigation: Lymphocytes

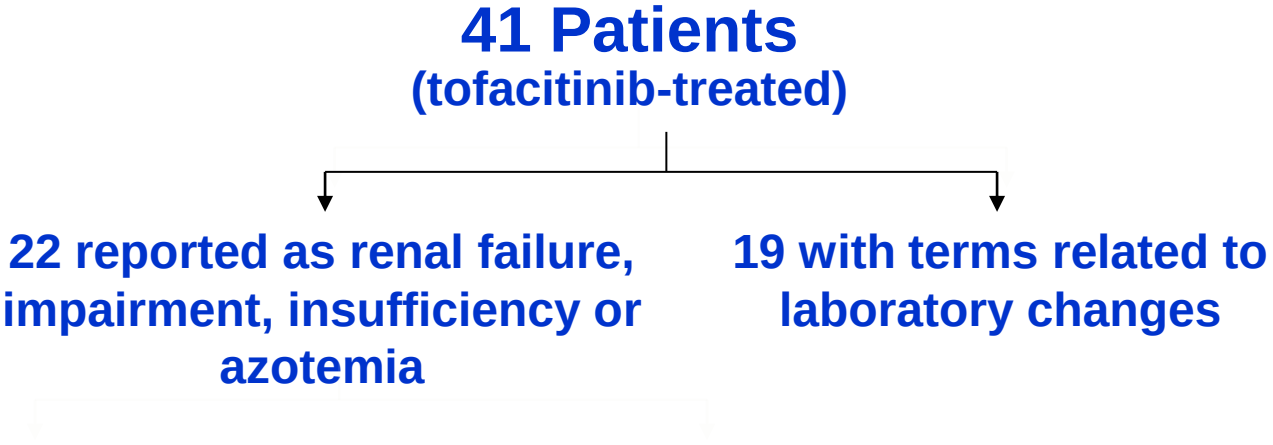
| **Lymphocytes** | |
|---|---|
| Dosage Modification | •Monitor at baseline and every 3 months thereafter |
| Warnings and Precautions | • Do not initiate tofacitinib for level of <500/$mm^3$<br>• Interrupt dose for confirmed level of <500/$mm^3$ |

# Mean Creatinine: Phase 3 Studies




Mean (± SE) creatinine levels (mg/dL) per Visit in Phase 3 Studies (Overall 0 to 12 Months)
**Data as of 29 March 2011**

# Evaluation of Renal Events




Data as of 29Mar2011

# Evaluation of Renal Events

**41 Patients**
**(tofacitinib-treated)**

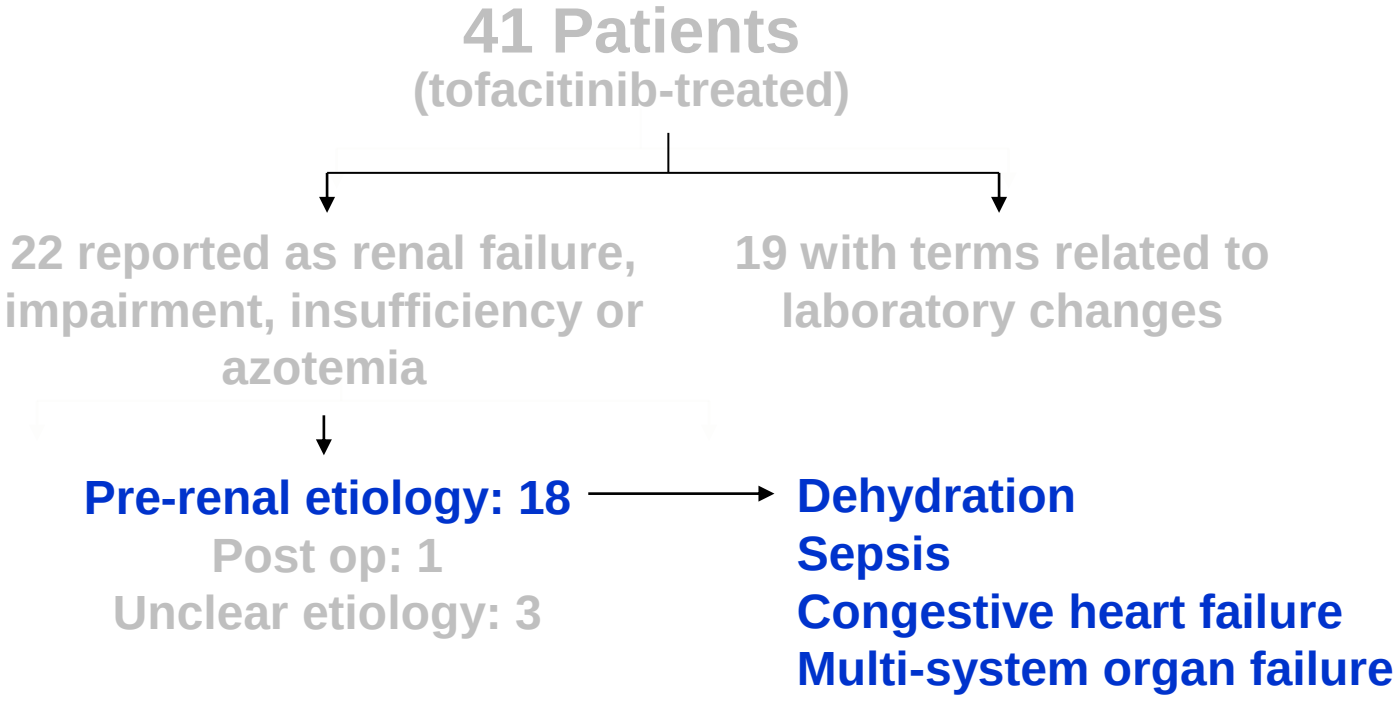
**22 reported as renal failure, impairment, insufficiency or azotemia**

**19 with terms related to laboratory changes**

**Pre-renal etiology: 18**
**Post op: 1**
**Unclear etiology: 3**

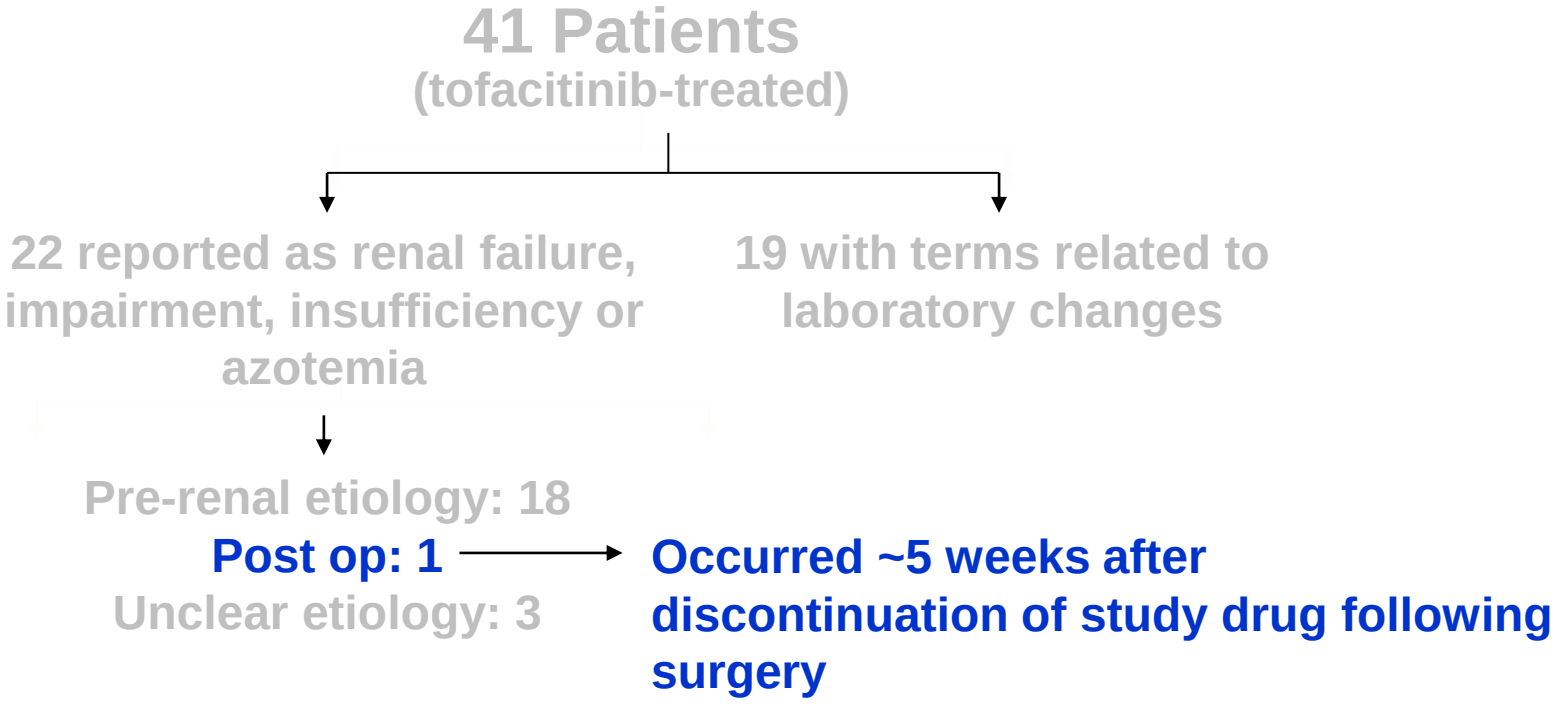
Data as of 29Mar2011

# Evaluation of Renal Events



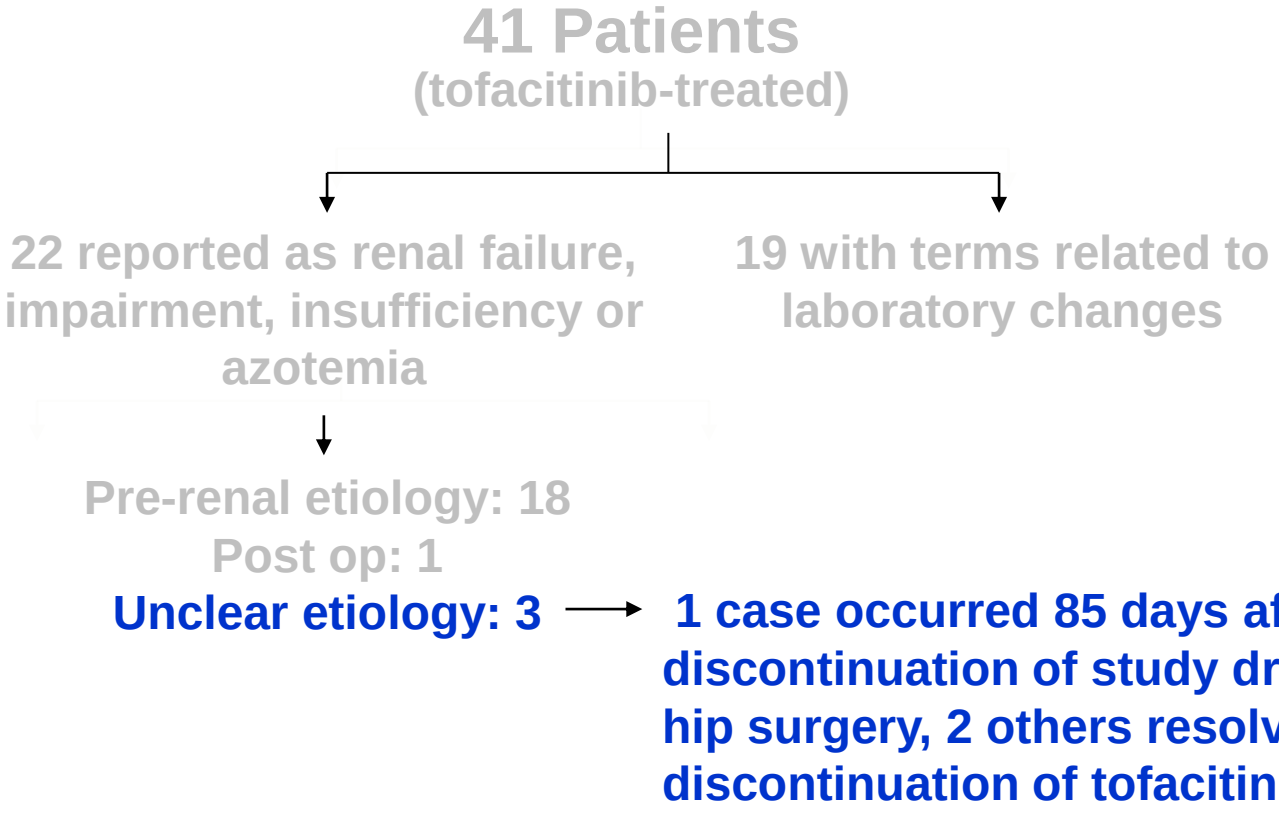

Data as of 29Mar2011

# Evaluation of Renal Events




Data as of 29Mar2011

# Evaluation of Renal Events




Data as of 29Mar2011

# Creatinine: Potential Mechanisms

- Exact mechanism unknown
- No evidence of nephrotoxicity in nonclinical studies or in the RA clinical development program
- No changes in serum creatinine, creatinine clearance, measured GFR or renal plasma flow in healthy volunteers
- No changes in tubular secretion of creatinine in healthy volunteers
- Increases in serum creatinine associated with inflammatory burden in RA patients
- Measured GFR study in RA patients is ongoing

# Risk Assessment: Creatinine

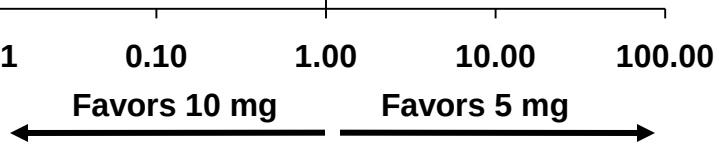
| Studies | Assessment |
|---|---|
| Ongoing (including LTE) and future clinical studies | Continued assessment of creatinine increases and renal adverse events |
| Mechanism study (ongoing) | Measured GFR study in RA patients |

# Safety Review Agenda

- Safety Database Overview
- General Safety
- Safety Topics of Special Interest
- Laboratory Changes
- Conclusions
  - Safety summary for tofacitinib 5 mg versus 10 mg BID

# Safety Summary for 5 mg versus 10 mg BID

| Endpoint | Comparison | Risk Ratio (95% CI) 10 mg / 5 mg | Incidence Rate (events/100 PY) 5 mg | 10 mg |
|---|---|---|---|---|
| All Cause Mortality | P3ALL | 0.79 | 0.553 | 0.439 |
| | LTE | 0.49 | 0.367 | 0.178 |
| Serious Infection | P3ALL | 0.92 | 3.217 | 2.97 |
| | LTE | 1.74 | 2.332 | 4.058 |
| Malignancy (excl. NMSC) | P3ALL | 1.59 | 0.553 | 0.879 |
| | LTE | 1.17 | 1.065 | 1.248 |
| NMSC | P3ALL | 1.66 | 0.332 | 0.55 |
| | LTE | 2.43 | 0.368 | 0.894 |
| Lung Cancer | P3ALL | 0.33 | 0.332 | 0.11 |
| | LTE | 3.23 | 0.147 | 0.475 |
| MACE | P3ALL | 1.49 | 0.443 | 0.659 |
| | LTE | 1.66 | 0.18 | 0.298 |
| GI Perforation | P3ALL | NA | 0 | 0.22 |
| | LTE | 1.21 | 0.147 | 0.178 |
| Herpes Zoster | P3ALL | 0.96 | 4.391 | 4.231 |
| | LTE | 1.16 | 4.089 | 4.736 |




Data as of 29SEP2011

# Safety Conclusions

- Safety profile of tofacitinib:
  - Well described, based on approximately 7000 pt-yrs of exposure
  - Similar to existing immunomodulatory therapies for RA, with specific differences as described
  - Rheumatologists are familiar with the appropriate management of patients on these RA therapies
- Pfizer is committed to continued diligence in assessing and mitigating risks
  - Ongoing pharmacovigilance
  - Risk management strategy that addresses key safety concerns
  - REMS

# Tofacitinib: Clinician's Perspective

Stanley Cohen, M.D.
Clinical Professor, Department of Internal Medicine
University of Texas Southwestern Medical School
Co-Director, Division of Rheumatology, Presbyterian Hospital Dallas
Co-Medical Director, Metroplex Clinical Research Center
Dallas, TX

# Tofacitinib: Benefits

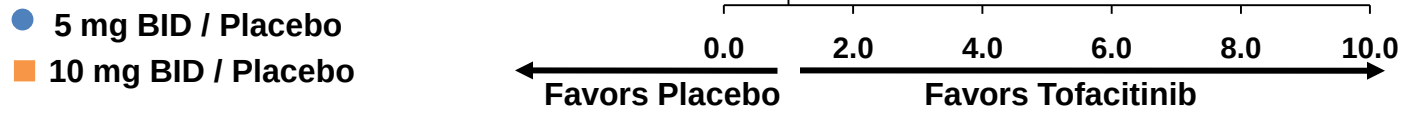
- **Novel MOA  targeting JAK proteins**
- **Oral therapy**
- **5 and 10 mg efficacy similar to approved biologics**
  - Improves signs and symptoms and patient quality of life
  - Inhibits radiographic progression
- **Immunogenicity is unlikely**
- **Onset of action is rapid**
- **Efficacy is durable**

# Tofacitinib: An Oral DMARD Option for RA Patients

- **Adverse events generally similar to approved biologic DMARDs with some differences**
- **Clinicians familiar with**
  - Adverse event profile
  - Necessary benefit risk evaluation
- **Fits well into current RA treatment paradigm**

# Clinically Meaningful Efficacy at Both 5 and 10 mg BID

| Endpoint | Comparison | Month 3 Probability Ratio (95% CI) | Proportion (%) Drug | Placebo |
|---|---|---|---|---|
| ACR20 | 5 mg vs Pbo | | 56.10 | 26.50 |
| | 10 mg vs Pbo | | 62.49 | |
| ACR50 | 5 mg vs Pbo | | 29.52 | 8.98 |
| | 10 mg vs Pbo | | 33.39 | |
| ACR70 | 5 mg vs Pbo | | 11.61 | 2.69 |
| | 10 mg vs Pbo | | 15.90 | |
| DAS28 ≤ 3.2 | 5 mg vs Pbo | | 15.18 | 4.16 |
| | 10 mg vs Pbo | | 19.92 | |
| DAS28 < 2.6 | 5 mg vs Pbo | | 6.55 | 1.83 |
| | 10 mg vs Pbo | | 9.39 | |
| HAQ-DI ≥ 0.3 | 5 mg vs Pbo | | 45.65 | 23.42 |
| | 10 mg vs Pbo | | 52.45 | |
| FACIT ≥ 4 | 5 mg vs Pbo | | 57.36 | 38.66 |
| | 10 mg vs Pbo | | 60.30 | |



# Conclusion

- **Tofacitinib: for inadequate responders to other DMARDs**
- **Possible alternative to biologic DMARDs in appropriate patients**

# Tofacitinib: Conclusions

**Yvonne Greenstreet, MB ChB**

**Senior Vice President**

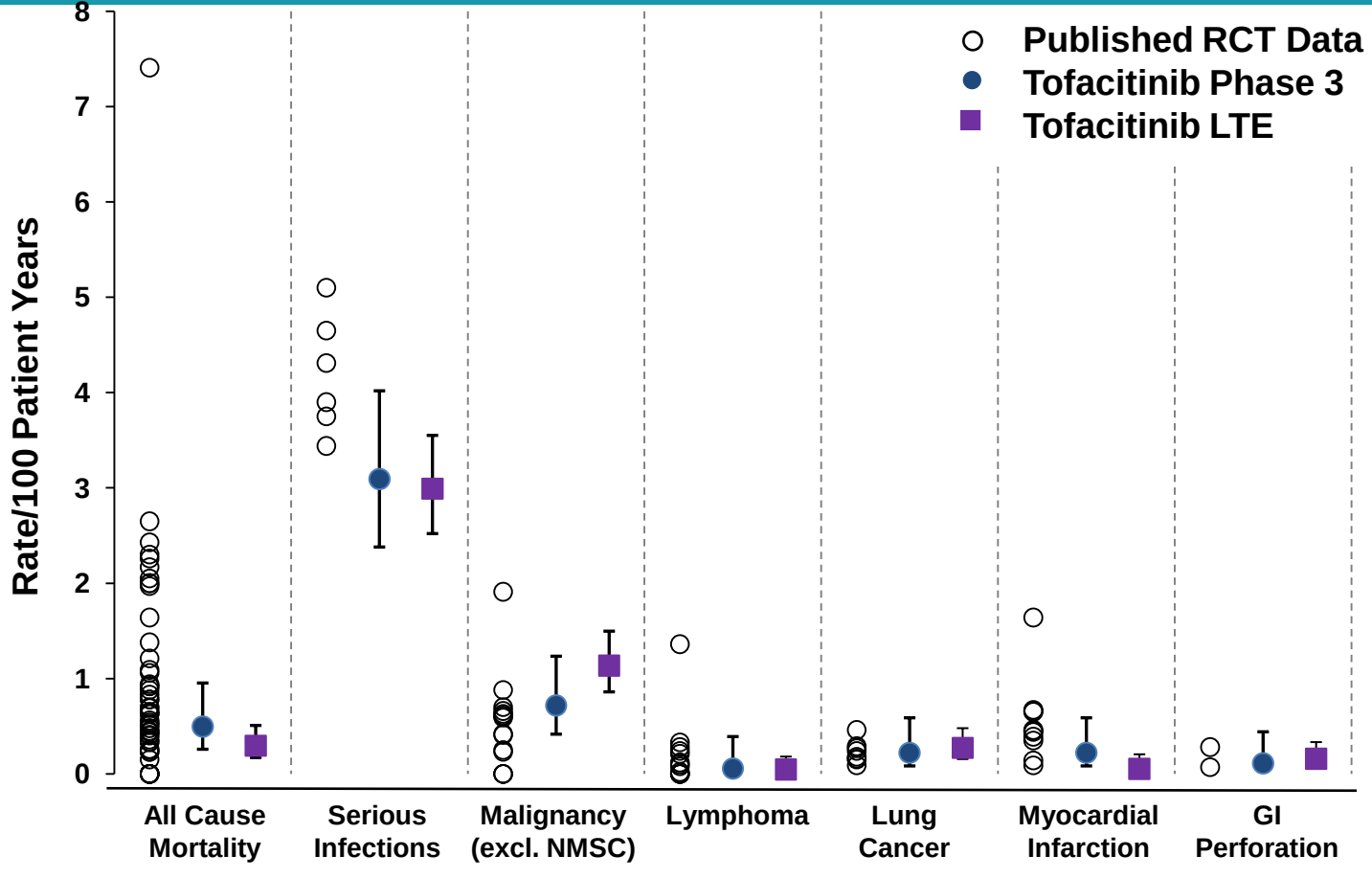
**Medicines Development Group, Specialty Care**

**Pfizer, Inc.**

# Summary

- Need for new therapies in RA
- Tofacitinib is a small molecule for oral use with innovative MOA targeting multiple cytokines
- Totality of the data supports efficacy for clinical and radiographic outcomes at 5 and 10 mg BID
- Safety profile
  - Characterized through ~4800 patient clinical development program
  - Similar to existing immunomodulatory therapies for RA, with specific differences

# Safety of Tofacitinib in Phase 3 and LTE vs. Published RCT Data



# Risk Management Strategy

- Clinical studies
- Post-marketing surveillance studies
- Risk Evaluation and Mitigation Strategy (REMS)

# Clinical Studies

| Studies | Outcomes of Interest |
|---|---|
| Long term extension studies | Malignancies, Serious and opportunistic infectious events, Cardiovascular safety with external adjudication of events of interest |
| Vaccination studies | Pneumococcal and influenza vaccination studies in patients receiving tofacitinib |
| Measured GFR Study in RA | Evaluation of the effect of tofacitinib on renal function |
| Cholesterol kinetic study | Study of the kinetics of cholesterol flux through the HDL/reverse cholesterol transport pathway in RA patients |

# Proposed Post-Marketing Surveillance Studies

- Patients actively monitored in five registries
  - CORRONA, a US Registry of >30,000 patients in 39 states
  - European registries (Germany, Sweden, UK) ~ 41,000 patients
  - OTIS, a US pregnancy registry with RA patients
- Multiple safety outcomes evaluated in each registry
  - CORRONA and EU registries: Malignancies, Cardiovascular Outcomes, Serious infections, Herpes Zoster, Pregnancy
  - OTIS registry: Pregnancy and infant outcomes

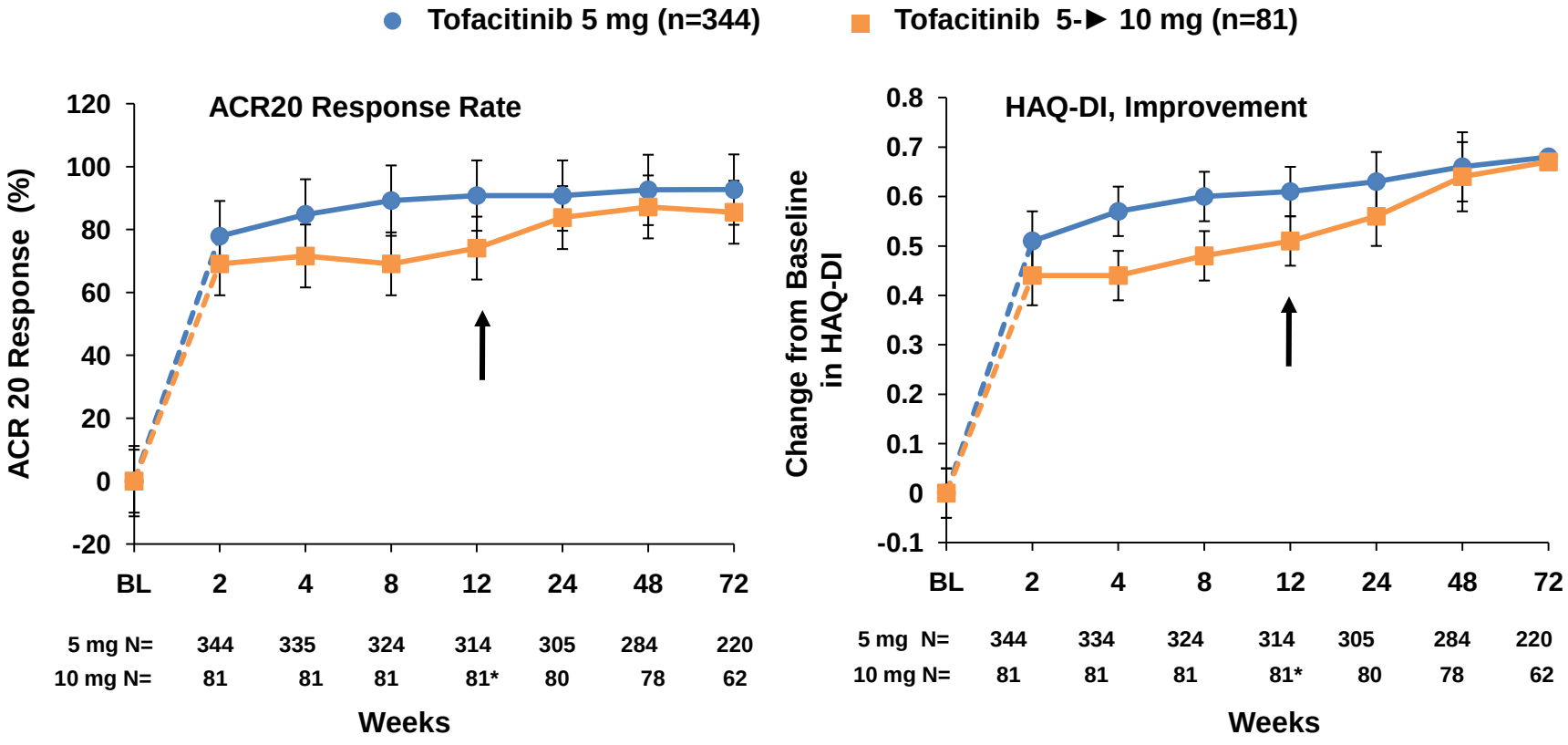
# Risk Mitigation

- Labeling
  - Boxed Warning: Serious Infections
  - Warnings and Precautions - Serious infections, Tuberculosis, Viral reactivation, Malignancy and lymphoproliferative disorder, Gastrointestinal perforations, Combination with biological DMARDs
  - Indicated for moderately to severely active RA with an inadequate response to one or more DMARDs
- REMS
  - Comprehensive educational materials for Healthcare Professionals
  - Dear HCP Letters
  - Information in journals and scientific meetings
  - Patient medication guide
  - Evaluation of effectiveness of the communication plan

# Conclusion

- Tofacitinib is an **innovative** treatment for RA patients
- A **positive benefit:risk** profile for both the 5 and 10 mg BID doses supports approval

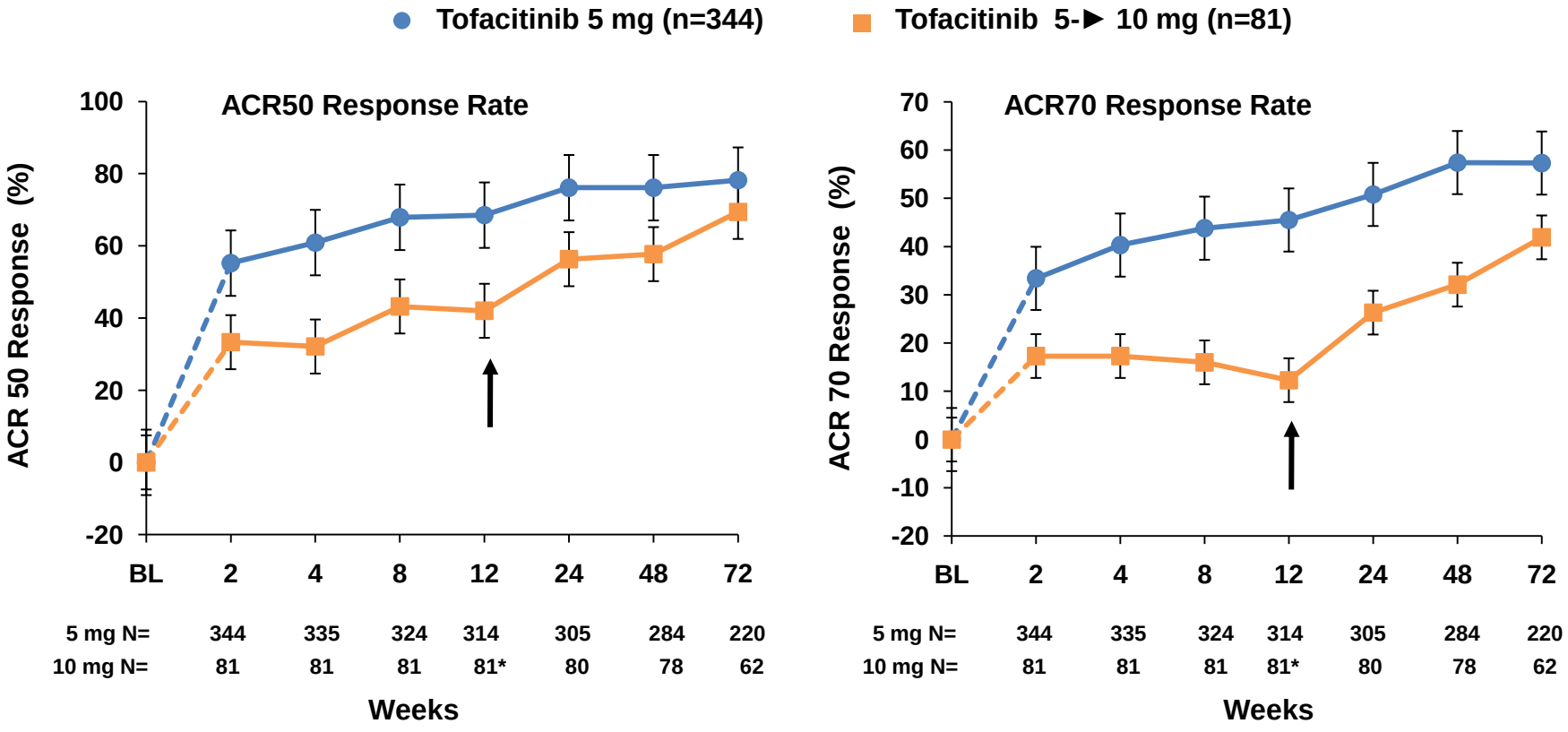
# ACR20 and HAQ-DI Responses Following Tofacitinib Dose Increase to 10 mg BID in Open-Label Extension




A3921041 patients started open-label tofacitinib at 5 mg BID.

*Based on investigator judgment, dose could be increased to 10 mg BID, beginning ~Week 12. Baseline (Week 0) is pre-treatment in the randomized controlled study

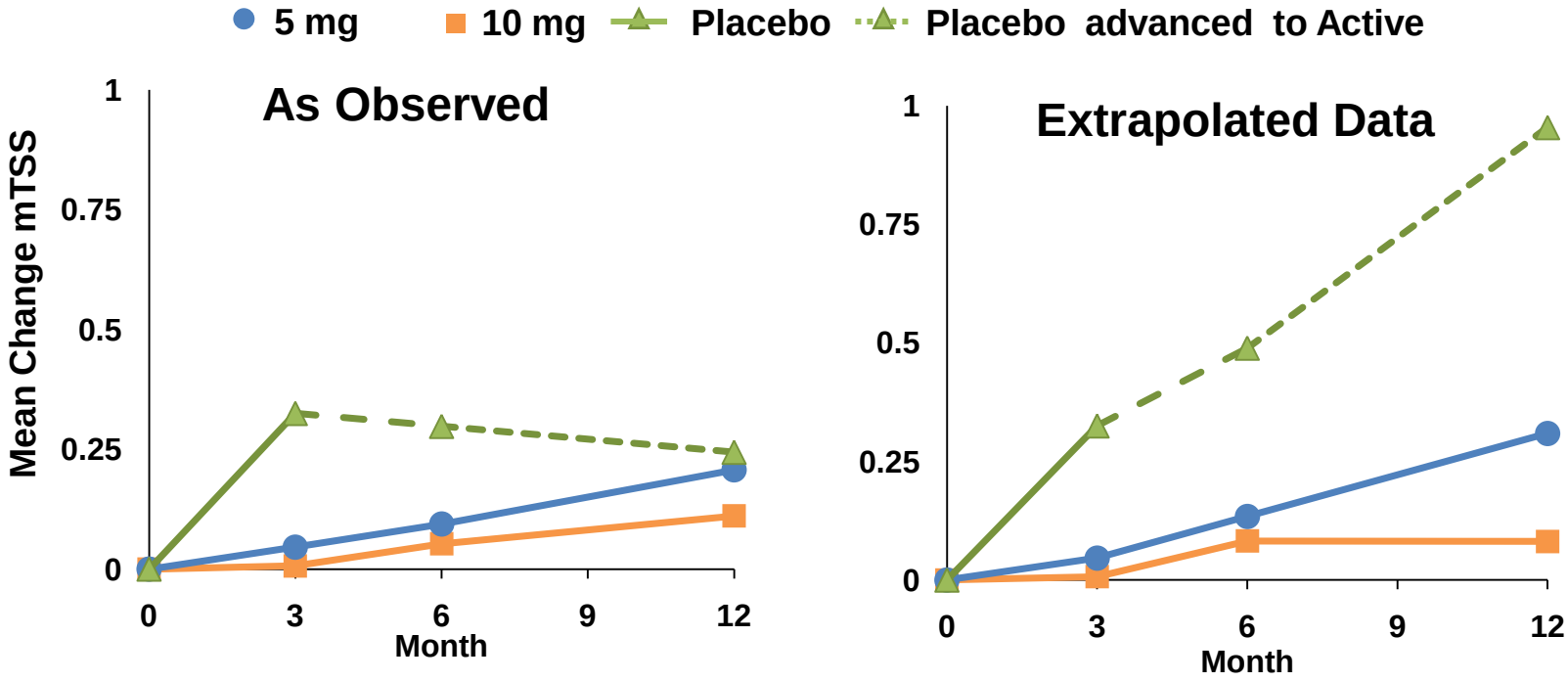
# ACR50/70 Responses Following Tofacitinib Dose Increase to 10 mg BID in Open-Label Extension




A3921041 patients started open-label tofacitinib at 5 mg BID.

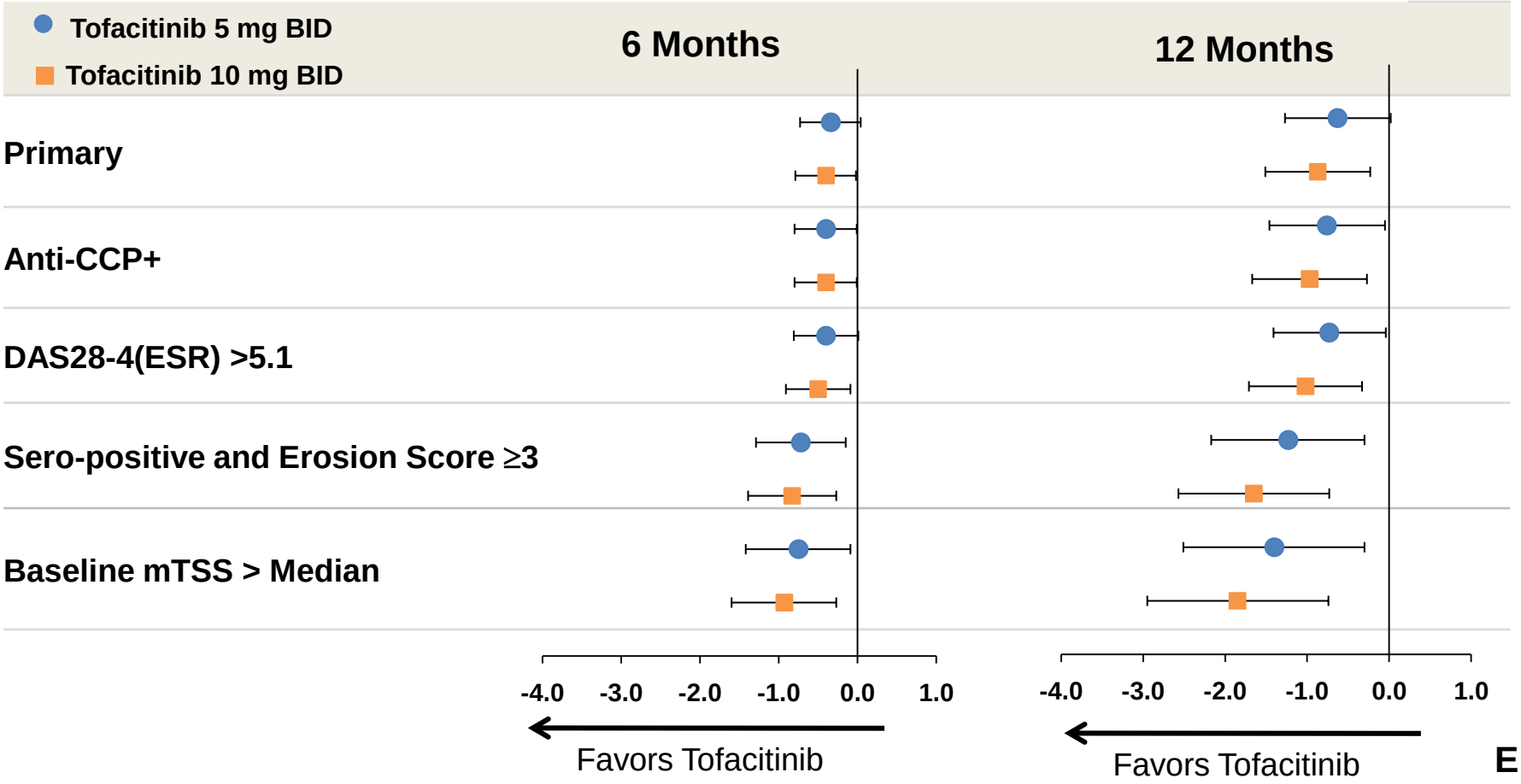
*Based on investigator judgment, dose could be increased to 10 mg BID, beginning ~Week 12. Baseline (Week 0) is pre-treatment in the randomized controlled study

# Observed Mean Change from Baseline in mTSS versus Linear Extrapolation by Treatment Group

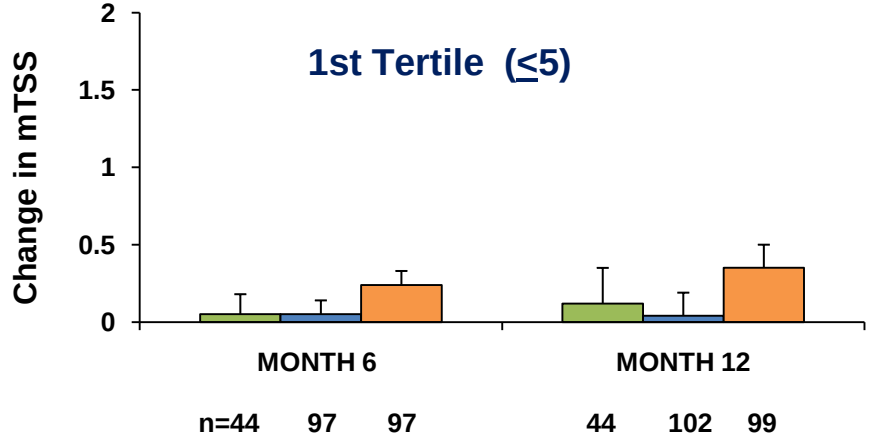



| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 5mg | 286 | 97 | 265 | 251 | 295 | 70 | 290 | 295 |
| 10mg | 295 | 70 | 277 | 258 | 286 | 97 | 277 | 286 |
| Placebo | 139 | 83 | 129 | 123 | 139 | 83 | 139 | 139 |

# Tofacitinib Treatment Effective in Patients with Risk Factors for Radiographic Progression



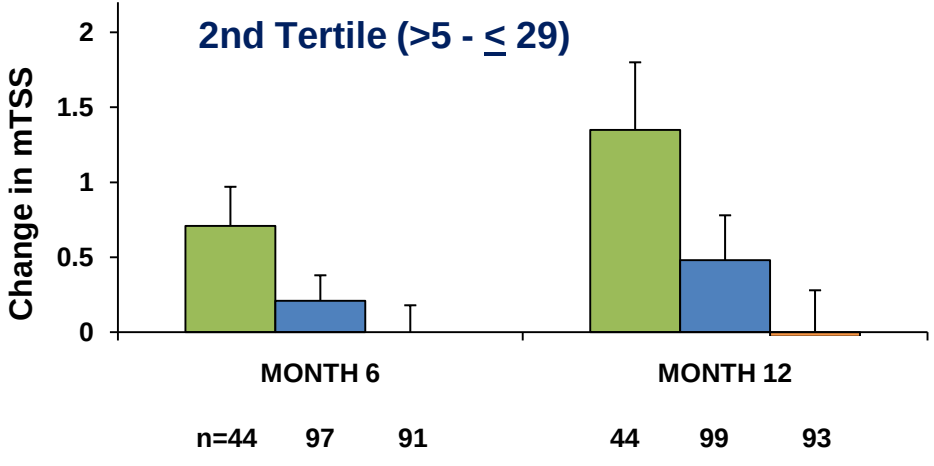
# Change in mTSS by Baseline mTSS-Defined Tertiles

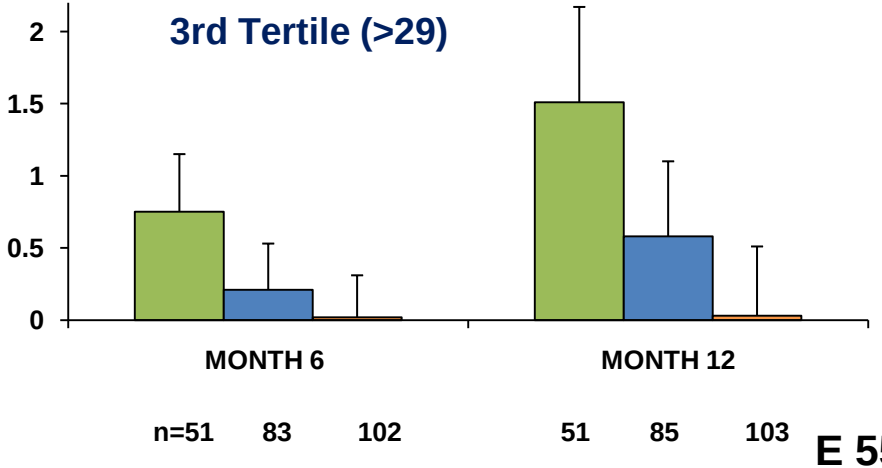



Placebo

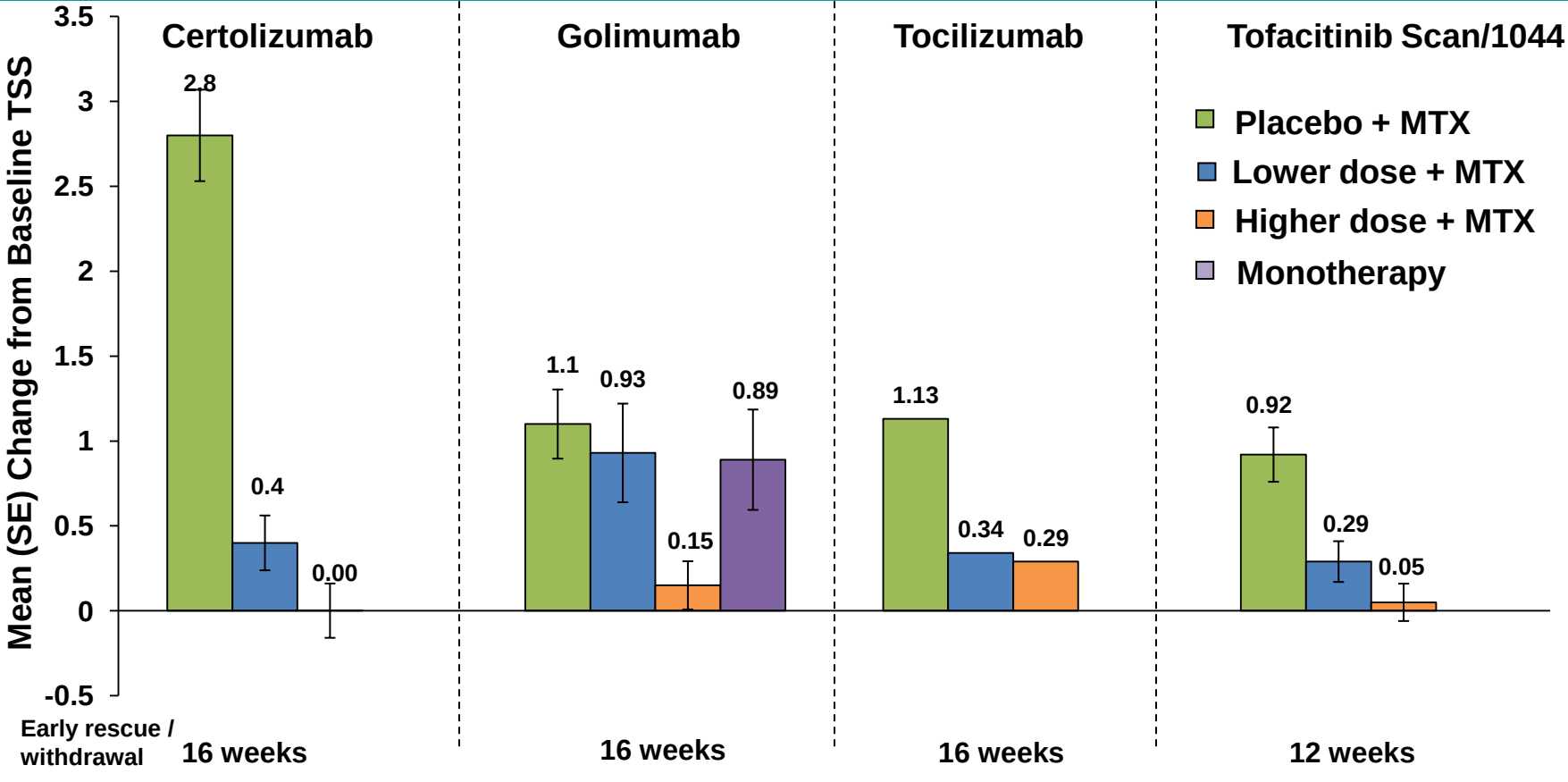
Tofacitinib 5 mg BID

Tofacitinib 10 mg BID



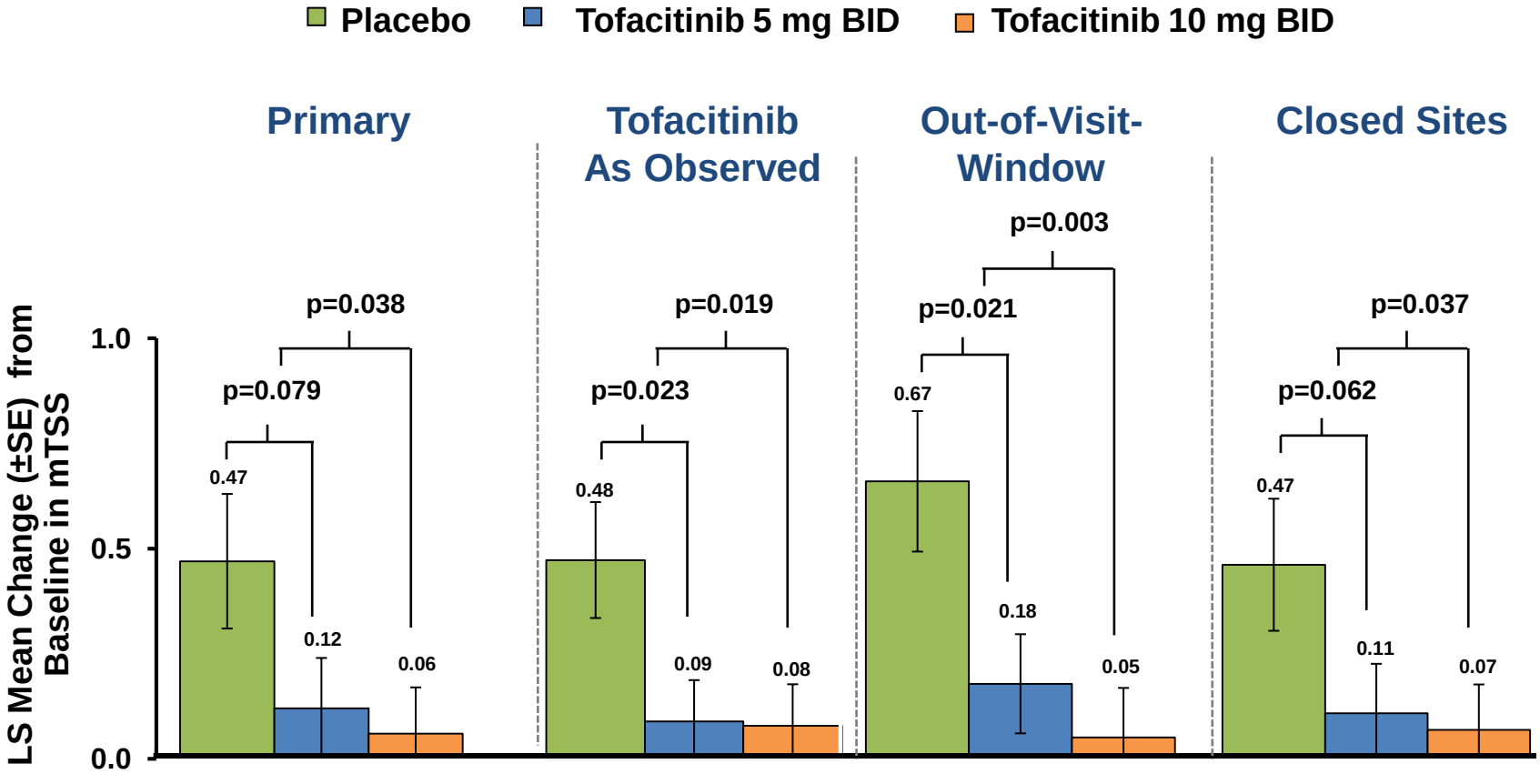



# Recent Biologic DMARD Structure Studies and Scan/1044: Month 12 Data




Actemra is mGSS; others are mTSS ; N – Number of patients ; NR – Non-responders

# Effect of Recovery of Excluded data on ANCOVA Change in mTSS (Month 6)




LS, least squares

# Herpes Zoster Vaccine

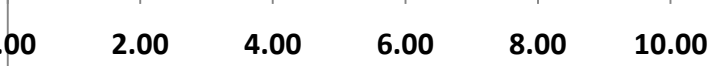
- Herpes zoster vaccine (Zostavax, Merck & Co., Inc.)
  - Live, attenuated virus vaccine
  - Licensed for prevention of herpes zoster in individuals 50 years of age and older
  - Advisory Committee on Immunization Practices (ACIP) recommends that patients who have the zoster vaccine indicated and who are anticipating immunosuppression should be vaccinated at least 14 days and ideally one month prior to treatment

http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax/pi2.pdf, accessed 21 Mar 2012

MMWR June 6, 2008/57(05);1-30

# Meta-analysis of Serious Infections in Clinical Trials

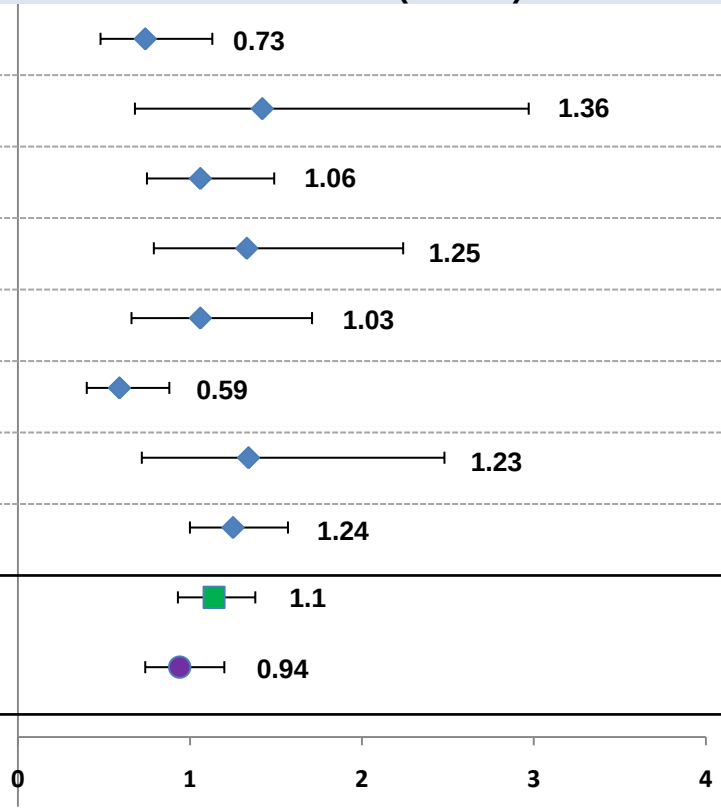
| Drug | Number of Trials | Serious Infections Rate / 100 PYO (95% CI) | Patients | Patient Years |
|---|---|---|---|---|
| Abatacept | 5 | 2.49 | 2608 | 1679 |
| Rituximab | 6 | 3.62 | 1920 | 1287 |
| Tocilizumab | 8 | 6.51 | 3087 | 1729 |
| Infliximab | 10 | 6.40 | 3740 | 3201 |
| Etanercept | 7 | 3.30 | 2213 | 3103 |
| Certolizumab pegol | 3 | 6.23 | 1384 | 889 |
| Golimumab | 6 | 5.31 | 2820 | 1648 |
| Adalimumab | 8 | 4.90 | 2335 | 1913 |
| TNF alpha inhibitor | 33 | 5.14 | 12802 | 10874 |
| Tofacitinib | 13 | 3.00 | 4791 | 6876 |




TE 232

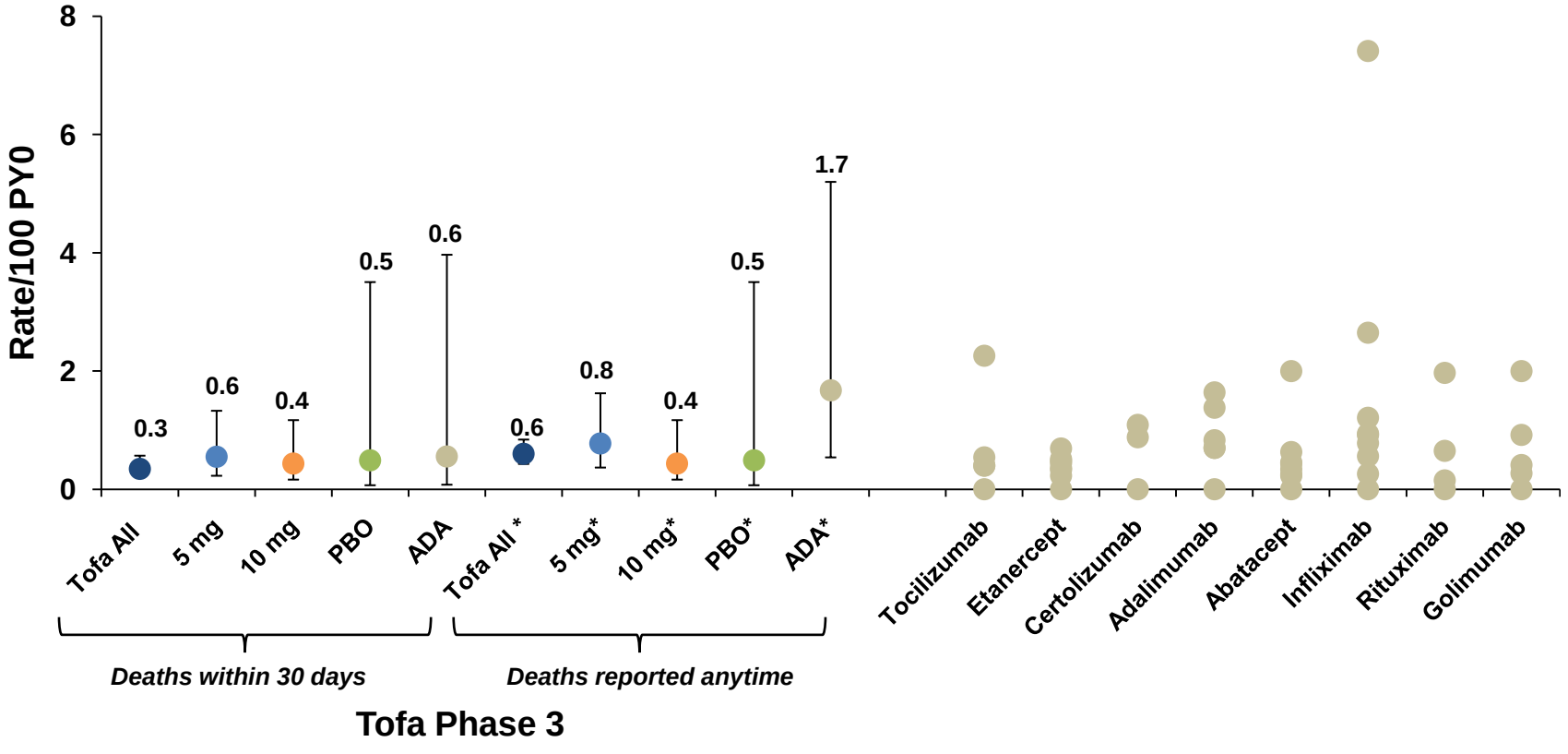
# Meta-analysis of Malignancy (excl. NMSC) in Clinical Trials

| Drug | Number of Trials | Malignancy Rate / 100 PYO (95% CI) | Patients | Patient Years |
|---|---|---|---|---|
| Abatacept | 6 | 0.73 | 3328 | 3702 |
| Rituximab | 2 | 1.36 | 1020 | 738 |
| Tocilizumab | 8 | 1.06 | 6825 | 3222 |
| Infliximab | 8 | 1.25 | 1859 | 2025 |
| Etanercept | 8 | 1.03 | 2574 | 5472 |
| Certolizumab | 6 | 0.59 | 2367 | 4065 |
| Golimumab | 5 | 1.23 | 2227 | 1284 |
| Adalimumab | 12 | 1.24 | 9228 | 8410 |
| TNF alpha inhibitor | 39 | 1.1 | 19110 | 21619 |
| Tofacitinib | 13 | 0.94 | 4791 | 6919 |




TE 266

# All Cause Mortality
# Comparison of Deaths Reported Within 30 days and Deaths Reported Anytime

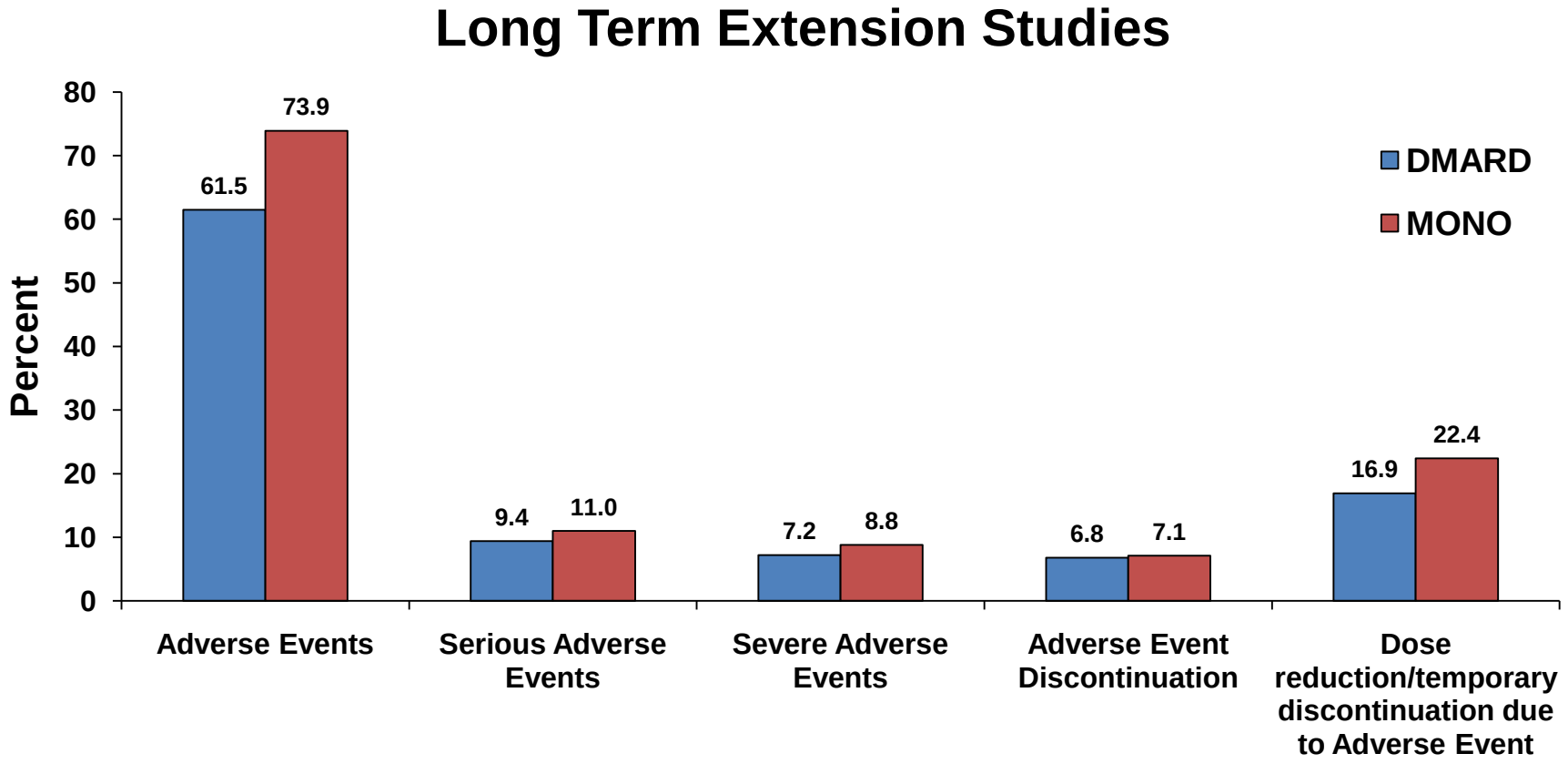



All Cause Mortality
Bars for CP indicate 95% Confidence Limits.
Dots for other drugs represent point estimates found in different published sources. Darker dots indicate repeat values.

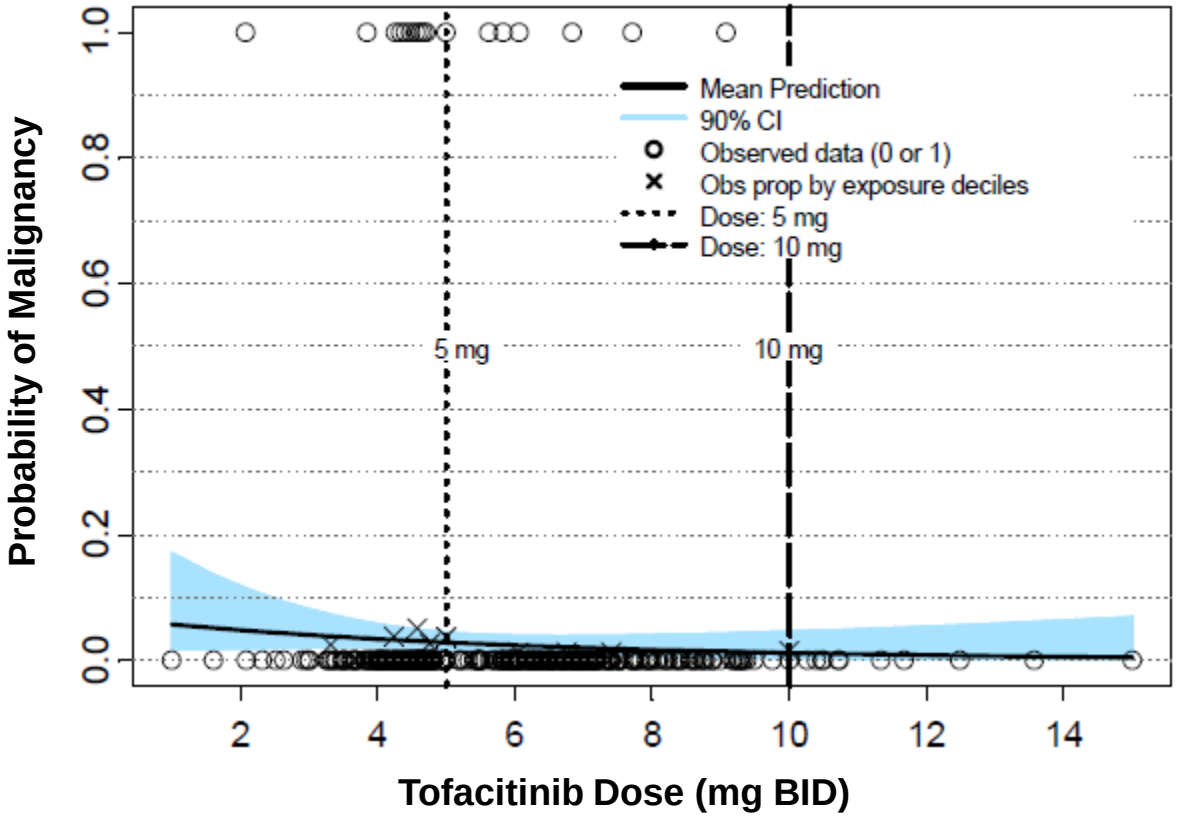
# Safety Summary: DMARD versus Monotherapy

- Comparable safety with few exceptions:
  - Increased herpes zoster rates on background DMARD (Phase 3)
    - 2.34/100 pt-yr for Monotherapy
    - 4.64/100 pt-yr for background DMARD
    - Few events in the Monotherapy group with overlapping confidence intervals
  - Increased transaminase elevations on background DMARDs
    - Likely attributable to the background DMARD therapy.

# Adverse Events: Background DMARD and Monotherapy

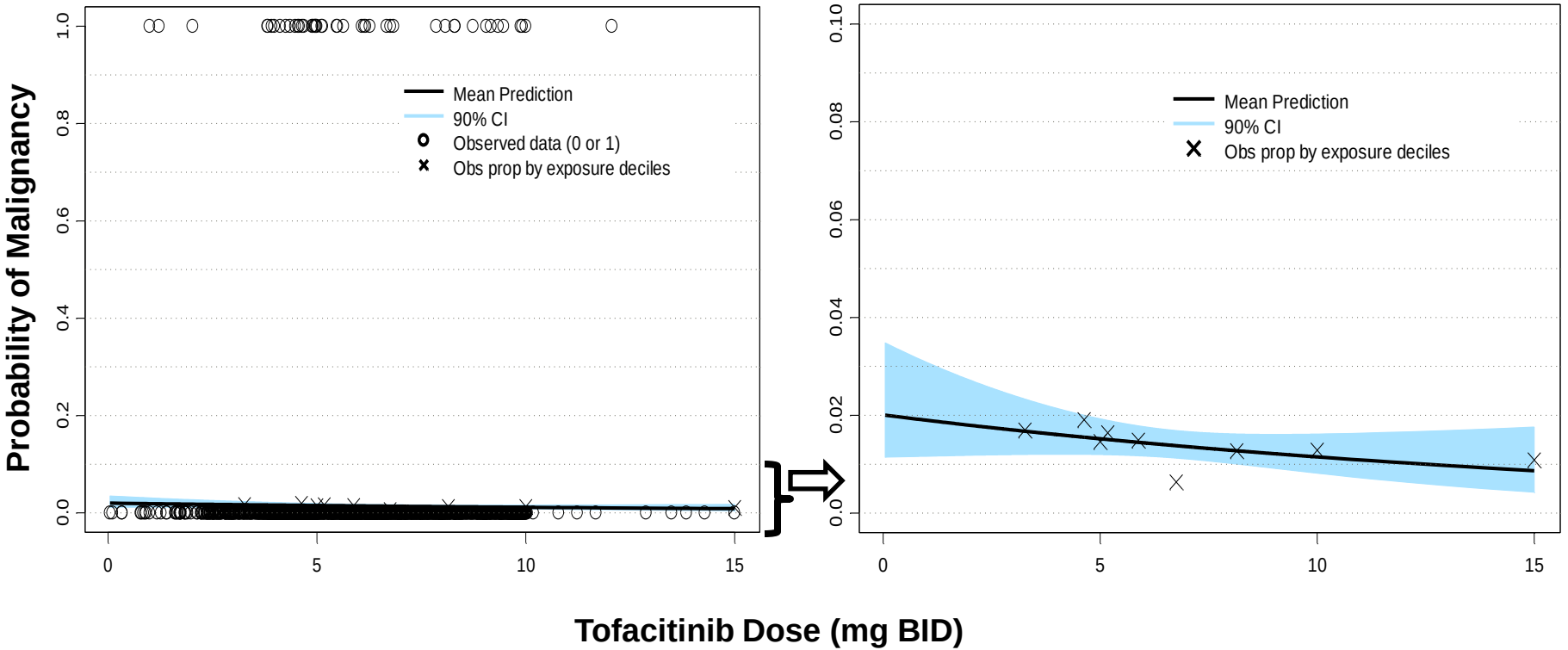


# Lack of Relationship between Dose and Malignancy



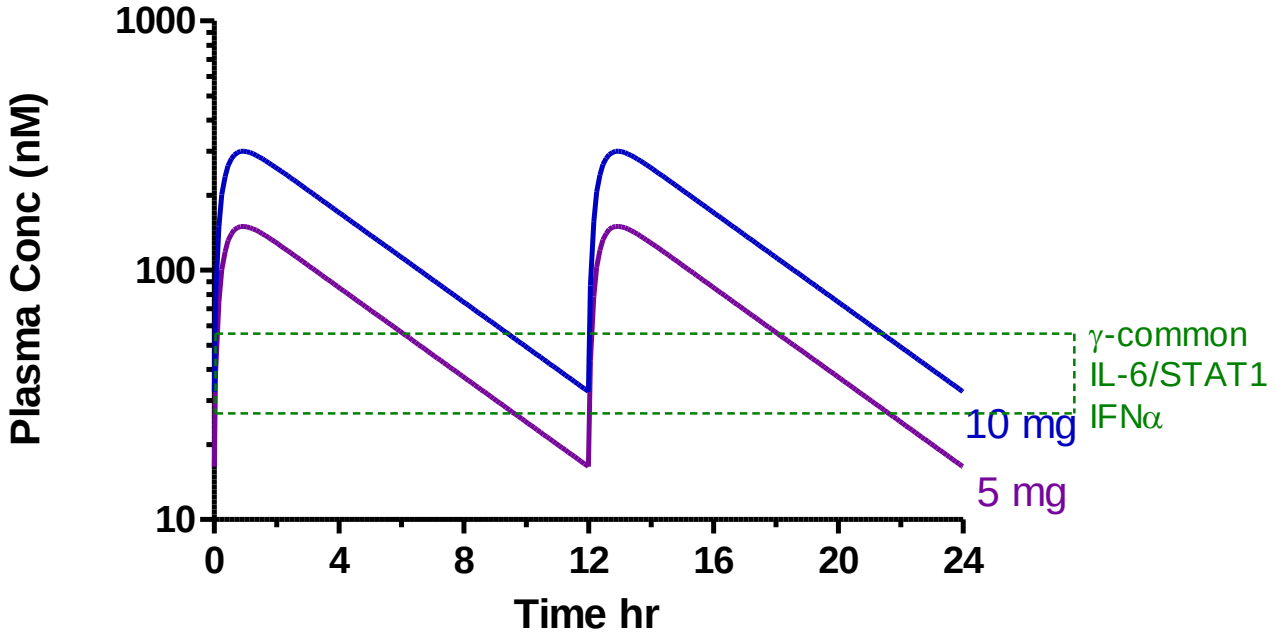

PK21

# Lack of Relationship between Dose and Malignancy




P2P3LTE data;
Tofacitinib dose is average dose in each patient from 1st dose to time of event , drop out or cut off date (Sep 29 2011)

# Tofacitinib Partially And Reversibly Inhibits Multiple JAK Dependent Cytokine Signaling Pathways




IL=interleukin; STAT=signal transducer and activator of transcription; IFN=interferon alpha

# Communications Plan for Healthcare Providers

- Dear HCP and Dear Pharmacist Letters
- Communications through journals and scientific meetings, clearly outlining the important risks of tofacitinib and the importance of assessing benefit-risk for each patient both prior to initiating therapy and while continuing on therapy
- The healthcare providers will include:
  - Rheumatologists and rheumatology healthcare providers
  - Infectious disease specialists who may be consulted about serious and other important infection
  - Gastroenterologists and hepatologists who may be consulted about gastrointestinal perforation and hepatic disease
  - Family practitioners, general practitioners, and internal medicine specialists, and emergency medicine specialists who may treat serious infections, gastrointestinal perforations, and hepatic disease